THE GENERAL PRACTICE MANUALS

CORONARY ARTERY DISEASE—*Ernst P Boas M D* and *Norman F Boas M D*

VASCULAR DISEASES IN CLINICAL PRACTICE—*Irving Sherwood Wright M D*

DIABETES MELLITUS IN GENERAL PRACTICE—*Arthur R Colwell M D*

HEADACHE—*Louis G Moench M D*

OFFICE IMMUNOLOGY (INCLUDING ALLERGY)—*Marion B Sulzberger M D* and *Rudolf Baer, M D* (editors)

ANESTHESIA IN GENERAL PRACTICE (2D EDITION)—*Stuart C Cullen M D*

RH ITS RELATION TO CONGENITAL HEMOLYTIC DISEASE AND TO INTRA GROUP TRANSFUSION REACTIONS—*Edith L Potter M D Ph D*

DIFFERENTIAL DIAGNOSIS OF JAUNDICE—*Leon Schiff Ph D M D*

TREATMENT OF THE PATIENT PAST FIFTY (3D EDITION)—*Ernst P Boas M D*

ENDOCRINE THERAPY IN GENERAL PRACTICE (6TH EDITION)—*Elmer L Sevringhaus M D*

NUTRITIONAL AND VITAMIN THERAPY IN GENERAL PRACTICE—*Edgar S Gordon M D*

OFFICE TREATMENT OF THE NOSE THROAT AND EAR (2D EDITION)—*A R Hollender M D*

OFFICE GYNECOLOGY (5TH EDITION)—*J P Greenhill M D*

OBSTETRICS IN GENERAL PRACTICE (4TH EDITION)—*J P Greenhill M D*

UROLOGY IN GENERAL PRACTICE (2D EDITION)—*Nelse F Ockerblad M D*

DERMATOLOGIC THERAPY IN GENERAL PRACTICE (3D EDITION)—*Marion B Sulzberger M D*, and *Jack Wolf M D*

SCARLET FEVER—*George F Dick M D D Sc* and *Gladys Henry Dick M D D Sc*

MANUAL OF PHYSICAL DIAGNOSIS (3D EDITION)—*Ellis B Freilich M D* and *George C Coe M D*

PICTORIAL HANDBOOK OF FRACTURE TREATMENT (2D EDITION)—*Eduard L Compere M D* and *Sam W Banks M D* assisted by *Clinton L Compere M D*

ARTERIAL HYPERTENSION (2D EDITION)—*Irvine H Page M D* and *Arthur Curtis Corcoran M D*

(OTHER TITLES IN PREPARATION)

ARTERIAL HYPERTENSION

ARTERIAL HYPERTENSION

Its Diagnosis and Treatment

by

IRVINE H PAGE M D

ARTHUR CURTIS CORCORAN M D

RESEARCH DIVISION OF THE
CLEVELAND CLINIC FOUNDATION CLEVELAND



THE YEAR BOOK PUBLISHERS INC

200 East Illinois Street Chicago

Reprinted with revisions September 1946
Second edition September 1949

PRINTED IN U S A

TO

DONALD D. VAN SLYKE

THIS BOOK IS

RESPECTFULLY AND AFFECTIONATELY

DEDICATED

Preface to the Second Edition

TIMES CHANGE. WE CHANGE WITH THEM So too should prefaces and introductions

As in the first edition this book is intended to be of use to those who undertake the care of patients suffering from arterial hypertension It is composed of recommendations prescriptions and technics of diagnosis which we consider important and prac tical These are the core and matter of the book From this it fol lows that we do not propose an academic treatise nor one which aims at exhausting either the topic or as we hope the reader

However the book is bound together by a *concept of the nature* of essential hypertension which constitutes its *form* It is an approximation of the truth. The extent to which it will be invalidated or confirmed is not of first importance It is intended only as a basis for practice and exposition

We do not know the essence of essential hypertension It is un likely that anyone will ever be able to offer a single and unitary concept of what seems to us its multiphasic mechanism Conse quently we visualize the disease as a process which is molded to varying forms by the patient his psyche and physique

The bibliographic references are not meant to be complete Their selection is aimed at making available to the reader articles which survey certain broad aspects of the field or which have special and topical interest.

The text has been either entirely rewritten or extensively revised A chapter has been added on the diagnosis and treatment of hypertension due to known or ascertainable causes The surge of interest in dietotherapy of hypertension is the occasion for a chapter on this topic also A section of one chapter is devoted to the technic and results of pyrogen treatment of malignant hypertension Mention is made of new drugs now under study The section on renal aspects of hypertension has been modified and we have added an appendix on some of the methods and procedures we use in the study of hypertension These additions have, of course required the abbreviation of those parts of the text which were of the least interest and use

The first to measure arterial pressure the Rev Stephen Hales observed in Statical Essays that We must be content in this our infant state of knowledge while we know in part only to imitate children who for want of better skill and abilities and of more proper materials amuse themselves with slight buildings In the meantime it would but ill become us in this our state of uncertainty to treat the errors and mistakes of others with scorn and contempt when we cannot but be conscious that we ourselves see things but as through a glass darkly and are very far from any pretentions to infallibility To which Amen!

Lastly our thanks to all the many who have helped in the preparation of this book and more particularly of the present edition We are particularly grateful to Dr Ernest Page of Berkeley for his suggestions on the toxemias of pregnancy and to Dr Robert Taylor our colleague and friend of many years for his pervasive and resourceful stimulation to thought and action Mrs Raymond Strattan continues to give her invaluable secretarial help To the publisher our fullest meed of praise and thanks

—I H P
—A C C

Table of Contents

SECTION I

SECTION II

SECTION III

SECTION IV

SECTION V

SECTION I

1 Normal Blood Pressure Classification of Hypertension

THE LEVEL of arterial blood pressure is relatively constant in normal people Still its range of variation is wide and it is much influenced by both internal and external environmental factors Some of these important to the physician in the evaluation of his measurements will be discussed shortly It is not surprising that observers are not agreed as to what level of blood pressure is to be considered normal in view of the many variables which affect it

Consequently the isolated finding of arterial hypertension is not sufficient evidence on which to make the diagnosis of essential hypertension By failing to search for other indications of disease the physician is often led into error by too great preoccupation with the level of arterial pressure Elevation of blood pressure alone does not constitute a disease but elevation of blood pressure which follows a definite course does Other signs and symptoms are often nonspecific elevation of arterial pressure then is the earliest and most characteristic sign of essential hypertension Recognition of a pathologically increased arterial pressure depends largely on a consideration of those factors most likely to alter the pressure from the physiologic basal level

FACTORS INFLUENCING ARTERIAL PRESSURE

A distinction should be drawn between casual measurements i e those made in office practice usually in the sitting position

and after a rest of no more than 15 minutes, and resting measurements made after 30–60 minutes of rest in the recumbent position The latter have much the same significance as basal measurements made after rest in the postabsorptive state Indeed the term basal blood pressure should be restricted to measurements in which the observer has definite proof of the maintenance of a basal state psychic and somatic, and is therefore not to be used lightly

The joint recommendations of the American and British Committees on Standardization of Blood Pressure Readings follow

1 *Blood pressure equipment*—The blood pressure equipment to be used whether mercurial or aneroid should be in good condition and calibrated at yearly intervals—more often if defects are suspected (Mercurial preferred—British Committee)

2 *The patient*—The patient should be comfortably seated (or lying—British Committee) with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface If readings are taken in any other position a notation of that fact should be made The patient should be allowed time to recover from any recent exercise or excitement There should be no constriction of the arm by clothes etc

3 *Position and method of application of the cuff*—A standard sized cuff containing a rubber bag 12 to 13 cm in width should be used A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 1 inch above the antecubital space and with the rubber bag applied over the inner aspect of the arm The cuff should be of such a type and applied in such a manner that inflation causes neither bulging nor displacement

4 *Significance of palpatory and auscultatory levels*—In all cases palpation should be used as a check on auscultatory readings. The pressure in the cuff should be quickly increased in steps of 10 mm Hg until the radial pulse disappears and then allowed to fall rapidly If the radial pulse returns at a higher level than that at which the first sound is heard the palpatory reading should be accepted as the systolic pressure otherwise the auscultatory reading should be accepted

5 *Position and method of application of stethoscope*—The stethoscope should be placed over the previously palpated brachial artery in

the antecubital space not in contact with the cuff No opening should exist between the lip of the stethoscope and the skin this should be accomplished with the minimum pressure possible. The hand may be pronated or supinated, depending on which position yields the clearest brachial pulse sounds

6 *Determination of systolic pressure* —The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated at a rate of 2 to 3 mm. Hg per second. The level at which the first sound regularly appears should be considered the systolic pressure unless, as pointed out above the palpatory level is higher in which event the palpatory level should be accepted. This should be noted.

7 *Determination of diastolic pressure and pulse pressure* —With continued deflation of the cuff the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure If there is a difference between that point and the level at which the sounds completely disappear the American Committee recommends that the latter reading should be regarded also as the diastolic pressure This should then be recorded in the following form RT* (or LT†) 140/80–70 or 140/70–0 If these two levels are identical, the blood pressure should be recorded as follows 140/70–70 The cuff should be completely deflated before any further determinations are made.

A basic technical problem in auscultatory measurement of arterial pressure is the width of the cuff A cuff which is too narrow for the arm size increases apparent pressure One index for selection of an adults rather than a childs cuff is body height of 50–54 in or more

Some of the variables of the determination may be briefly noted From within out the first of these is the form of the pulse wave A round full wave will pass a point of slight compression where a thin peaked wave as in tachycardia may be arrested thin waves tend to yield low values Within the vessel wall medial arteriosclerosis may increase rigidity and resistance to lateral pressure so that falsely high values are obtained The error in such cases

---

*Right arm.

†Left arm.

does not usually exceed 10 mm The resistance of the extravascular tissues of the arm is normally canceled by application of a cuff of standard width (12 cm) so this factor may be disregarded In the obese *still larger cuffs (16 cm width)* may have to be applied to cancel this resistance for with a standard cuff many people with fat arms yield measurements of auscultatory pressure which exceed true arterial pressure In children smaller cuffs should be used (6 cm in infants, 9 cm at ages 4–8 years) Some people possibly those with tendency to the scalenus anticus syndrome can at will or when the arm is placed in the appropriate position obliterate the axillary artery and thus delude the hasty examiner while others during voluntary or involuntary contraction of the arm muscles can so increase the tissue resistance as to increase the apparent level of pressure

However with all its sources of error the determination is extraordinarily precise Systolic pressure is probably underestimated a few millimeters (5–10) Diastolic pressure at the fourth phase of *muffled sound is usually overestimated about 8 mm Hg* at the phase of complete disappearance of sound it corresponds approximately to radial diastolic pressure

Differences of pressure between the two arms of 10 mm Hg systolic and 5 mm diastolic are common among normotensives at the higher pressures of hypertension these differences are more obvious The right arm usually yields the higher readings No concern need be felt when the asymmetry is of this order even when its consistent presence establishes it as due to some factor other than minor variations of central arterial pressure or changes of local vasomotor activity Larger asymmetries of pressure demand further examination Such may arise from marked dilatation of the aorta *from hyperplastic cushions of fibrous and* atherosclerotic tissue at the mouths of the innominate or subclavian arteries or *from partial rupture of the aorta A cervical rib* radiographically demonstrable or the scalenus anticus syndrome or postural sub

clavian compression may account for wide pressure differences which will disappear with extension of the arm Hemiplegia alone even with extensive muscular wasting or spasm does not satisfactorily account for more than minor differences Thus major differences of pressure demand explanation They should be looked for by taking the pressure in both arms at some time during the course of observation Otherwise as in a scalenus syndrome arterial hypertension may be missed to the later embarrassment of the physician

Alam and Smirk and Kilpatrick have emphasized the *difference* (supplemental blood pressure) between basal blood pressure (readings obtained under basal conditions) and casual blood pressure (readings made under ordinary clinical conditions) Although the distinction is valuable in investigation it does not have a definite application in practice largely because of the difficulties of maintaining truly basal conditions in hypertensive subjects

An extended discussion of the causes of variations in pressures may be found in an excellent chapter by Allen The following circumstances are commonly associated with *moderate changes in* pressure

1 Posture Assumption of the erect posture causes a fall in systolic pressure from 5 to 40 mm about 10 seconds after the change In about 30 seconds it may have regained or exceeded the recumbent level The same type of reaction occurs when the patient is tilted but the drop is greater and recovery less complete Diastolic pressure rises 4 mm Hg or more on standing in half of a group of normal subjects Thus the net effect of standing or of being tilted to a vertical position is usually a moderate decrease of pulse pressure (Currens) *When the arm is allowed to hang by the side* or when femoral pressure is measured during standing gravity increases the measurements by as much as 10 mm Hg

2 Sleep Usually sleep causes a fall in pressure Some observers think that bad dreams and restless sleep actually cause a rise It is known with some certainty that systolic pressure is minimal at the

does not usually exceed 10 mm The resistance of the extravascular tissues of the arm is normally canceled by application of a cuff of standard width (12 cm), so this factor may be disregarded In the obese, still larger cuffs (16 cm width) may have to be applied to cancel this resistance, for with a standard cuff many people with fat arms yield measurements of auscultatory pressure which exceed true arterial pressure In children smaller cuffs should be used (6 cm in infants, 9 cm at ages 4–8 years) Some people possibly those with tendency to the scalenus anticus syndrome can at will or when the arm is placed in the appropriate position obliterate the axillary artery and thus delude the hasty examiner while others during voluntary or involuntary contraction of the arm muscles can so increase the tissue resistance as to increase the apparent level of pressure

However with all its sources of error the determination is extraordinarily precise Systolic pressure is probably underestimated a few millimeters (5–10) Diastolic pressure at the fourth phase of muffled sound is usually overestimated about 8 mm Hg at the phase of complete disappearance of sound it corresponds approximately to radial diastolic pressure

Differences of pressure between the two arms of 10 mm Hg systolic and 5 mm diastolic are common among normotensives at the higher pressures of hypertension these differences are more obvious The right arm usually yields the higher readings No concern need be felt when the asymmetry is of this order even when its consistent presence establishes it as due to some factor other than minor variations of central arterial pressure or changes of local vasomotor activity Larger asymmetries of pressure demand further examination Such may arise from marked dilatation of the aorta from hyperplastic cushions of fibrous and atherosclerotic tissue at the mouths of the innominate or subclavian arteries or from partial rupture of the aorta A cervical rib radiographically demonstrable or the scalenus anticus syndrome or postural sub

others lowers it. There appears to be no more than a transient action. The effects of nicotine and of smoking on blood pressure and other circulatory functions have been painstakingly studied by Grace Roth

12 Weight Obesity is usually if not always associated with slightly elevated arterial pressure Use of the 13 cm cuff for measurement of the pressure has led to error in the reading because the increased pressure required to compress the larger mass of tissue is reflected in a higher arterial pressure reading But besides this accurate measurement by the intra arterial method shows a slight increase in some obese but otherwise normal persons At the very least, obesity causes an increase in the work of the heart This with other factors not as obvious accounts for the increased rate of mortality and possibly for some of the real increase in arterial tension The effect of severe loss of weight is much less equivocal It is almost always associated in otherwise normal persons with a fall of blood pressure

13 Body build. The evidence on the effect of body build in arterial pressure is conflicting Visceroptotic persons and those with neurocirculatory asthenia usually have low arterial pressure The sthenic habitus often is associated with higher pressures than the asthenic Aside from these more or less pronounced types an accurate correlation of body build height and surface area with arterial pressure cannot be established

14 Climate and temperature Their role has been a subject of much discussion In Europeans who have moved to China and the tropics arterial pressure seems to be 10 *mm* lower both systolic and diastolic but whether this is due to climate alone is uncertain In warm weather blood pressure tends to fall

15 Environment. Ayman and Goldshine have shown in striking manner the effect of the environment of a clinic on blood pressure in a group of hypertensives Thirty per cent showed systolic pressures 40 *mm* Hg or more lower when measured in the home

fourth hour of sleep and rises slightly before waking and then abruptly after waking to a point equal to that of the first hour of sleep Diastolic pressure shows a like but lesser change The fall is believed to be due largely to fall in pulse rate

3 Diurnal variations *The pressure rises gradually during the* day, reaching a maximum about 6 or 7 P M (15–20 mm Hg rise), then falling during the night

4 Emotion Expressed or repressed, emotion may cause large rises in pressure, as every examiner must know

5 *Muscular effort Systolic pressure may be greatly increased* sometimes as much as 60 mm Hg during effort, diastolic pressure is decreased by moderate and increased by severe exercise

6 Meals Usually eating is followed by a rise of 10 mm Hg systolic and about 5 mm Hg diastolic

7 *Difference in arterial pressure in two arms Differences may* be significant, and blood pressure should be measured in both arms at the initial examination Close adduction may increase and hyperabduction decrease apparent systolic pressure Measurements are best made with the arms abducted 45–90 degrees and for *comparison, in the same relative position*

8 Menstruation and pregnancy Menstruation does not appear to have any significant effect on blood pressure During pregnancy frequently the arterial pressure falls from the fourth to the ninth lunar month to rise again in the tenth month It is usually normal *during the first week of the puerperium*

9 Constipation This seems to have no effect It is of interest that straining by increasing intrathoracic and intra abdominal pressure puts stress on the arteries of the arms legs and skin but the more vital arteries of the thorax abdomen and central nervous system are protected against the strain

10 Alcohol Being a vasodilator alcohol may cause some fall in blood pressure which is at times severe during deep intoxication

11 Tobacco *In some persons smoking raises pressure and in*

others lowers it. There appears to be no more than a transient action The effects of nicotine and of smoking on blood pressure and other circulatory functions have been painstakingly studied by Grace Roth.

12 Weight Obesity is usually if not always associated with slightly elevated arterial pressure Use of the 13 cm cuff for measurement of the pressure has led to error in the reading because the increased pressure required to compress the larger mass of tissue is reflected in a higher arterial pressure reading But besides this accurate measurement by the intra arterial method shows a slight increase in some obese but otherwise normal persons At the very least, obesity causes an increase in the work of the heart This with other factors not as obvious accounts for the increased rate of mortality and possibly for some of the real increase in arterial tension The effect of severe loss of weight is much less equivocal It is almost always associated in otherwise normal persons with a fall of blood pressure

13 Body build The evidence on the effect of body build in arterial pressure is conflicting Visceroptotic persons and those with neurocirculatory asthenia usually have low arterial pressure The sthenic habitus often is associated with higher pressures than the asthenic Aside from these more or less pronounced types an accurate correlation of body build height and surface area with arterial pressure cannot be established

14 Climate and temperature Their role has been a subject of much discussion In Europeans who have moved to China and the tropics arterial pressure seems to be 10 mm lower both systolic and diastolic, but whether this is due to climate alone is uncertain In warm weather blood pressure tends to fall

15 Environment Ayman and Goldshine have shown in striking manner the effect of the environment of a clinic on blood pressure in a group of hypertensives Thirty per cent showed systolic pressures 40 mm Hg or more lower when measured in the home

fourth hour of sleep and rises slightly before waking and then abruptly after waking to a point equal to that of the first hour of sleep Diastolic pressure shows a like but lesser change The fall is believed to be due largely to fall in pulse rate

3 Diurnal variations The pressure rises gradually during the day, reaching a maximum about 6 or 7 P M (15–20 mm Hg rise), then falling during the night

4 Emotion Expressed or repressed emotion may cause large rises in pressure, as every examiner must know

5 Muscular effort Systolic pressure may be greatly increased sometimes as much as 60 mm Hg during effort, diastolic pressure is decreased by moderate and increased by severe exercise

6 Meals Usually eating is followed by a rise of 10 mm Hg systolic and about 5 mm Hg diastolic

7 Difference in arterial pressure in two arms Differences may be significant and blood pressure should be measured in both arms at the initial examination Close adduction may increase and hyperabduction decrease apparent systolic pressure Measurements are best made with the arms abducted 45–90 degrees and for comparison, in the same relative position

8 Menstruation and pregnancy Menstruation does not appear to have any significant effect on blood pressure During pregnancy frequently the arterial pressure falls from the fourth to the ninth lunar month to rise again in the tenth month It is usually normal during the first week of the puerperium

9 Constipation This seems to have no effect It is of interest that straining by increasing intrathoracic and intra abdominal pressure puts stress on the arteries of the arms legs and skin but the more vital arteries of the thorax abdomen and central nervous system are protected against the strain

10 Alcohol Being a vasodilator alcohol may cause some fall in blood pressure which is at times severe during deep intoxication

11 Tobacco In some persons smoking raises pressure and in

ment are more standardized but on the whole they certainly are not far from what routine experience has taught to be consistent with health Table 2 gives average values for children

Some clinicians set the range in normal men and women at 90–120 mm Hg systolic and 60–80 mm Hg diastolic Others

TABLE 1—BLOOD PRESSURE IN HEALTHY MEN OF ALL BUILDS (SYMONDS)

AGE YR	SYSTOLIC PRESSURE MM (150 419 CASES)	DIASTOLIC PRESSURE MM (60 733 CASES)	PULSE PRESSURE MM
15 to 19	123 5	79 5	44 0
20 to 24	124 2	80 5	43 7
25 to 29	124 5	81 5	43 0
30 to 34	125 1	82 3	42 8
35 to 39	125 3	83 3	42 0
40 to 44	126 4	84 0	42 4
45 to 49	129 2	84 7	43 4
50 to 54	130 2	85 9	44 3
55 to 59	133 5	86 8	46 7
60 and over	135 2	86 9	48 3

TABLE 2—BLOOD PRESSURE IN CHILDREN (JUDSON AND NICHOLSON)

AGE YR	SYSTOLIC PRESSURE MM	DIASTOLIC PRESSURE MM	PULSE PRESSURE MM
3	92 0	58 4	33 6
4	92 6	61 7	30 9
5	91 6	60 0	31 6
6	93 8	63 5	30 3
7	87 9	64 2	23 7
8	93 0	59 6	33 4
9	91 7	62 2	29 5
10	99 0	64 0	34 4
11	95 8	62 3	33 5
12	99 9	59 6	40 3
13	104 0	63 2	40 8
14	105 8	63 7	42 1
15	99 6	61 8	37 7

believe 110–140 systolic and 70–90 diastolic are closer to normal There is disagreement as to whether arterial pressure normally rises as people grow older A minority holds that the mature blood pressure level is reached at about the time of adolescence and then does not vary significantly throughout the rest of life The majority finds that systolic mean and pulse pressures rise gradually from 40 to 62 years then rapidly from 62 to 85 The diastolic pressure

by the patient than when measured in the clinic by the physician Twenty four per cent showed diastolic readings 20 mm Hg or more lower

16 Fever Arterial pressure may be increased during a chill whereas fever is usually associated with decreased pressure which may persist for a day or two after the fever has subsided The chief cause of the decrease is arteriolar vasodilation which may be so extensive as to increase renal blood flow by more than 100 per cent (See pyrogen treatment p 328)

17 Nutrition Although as noted previously correction of obesity by undernutrition usually lowers pressure as does undernutrition in normal people an interesting transitory hypertension was observed under the specific deficiencies prevailing in prison camps of the Far East Its mechanism is obscure and it does not parallel European experience, where in Leningrad in 1942–43 hypertension is supposed to have been frequently precipitated in severe form by re feeding of the semistarved populace

Just as one increase of arterial pressure does not mean that essential hypertension is present or imminent, so one or even several observations in the normal range do not exclude it Blood pressure varies greatly even in the so called fixed stage of essential hypertension Ayman s experience and we can underscore it is that the more frequent the observations the greater the fluctuations No patient observed by him had fixed nonfluctuating hypertension The diastolic pressure fluctuated proportionately as much as the systolic

Normal Arterial Pressure

Despite the fluctuations which so commonly occur it is still possible to arrive at an average figure which is clinically useful Table 1 shows average values for blood pressure readings from a large group of insurance applicants Some investigators would find these averages too high as they may be when conditions of measure

wide variety of other morbid conditions may play an important part in producing it thus drawing attention to the fact that a painstaking search for the mechanism by which the arterial pressure is elevated is a necessary part of the study of all patients with hypertension. Often these underlying diseases are remediable To aid in calling to mind their wide variety the following tabulation was prepared

CLASSIFICATION OF HYPERTENSION

Renal

A Affections of vessels

Arteriosclerosis	Vascular anomalies and obstructions (embolism, venous or arterial thrombosis, aneurysm tumor)
Arteritis	
Panarteritis nodosa	
Visceral lupus erythematosus	
Scleroderma	

B Affections of parenchyma

Acute nephritis	Hypernephroma
Chronic nephritis	Ectopia
Pyelonephritis	Toxemia of pregnancy
Hydronephrosis	X ray lesions
Polycystic disease	Renal stones
Amyloidosis	Hypogenesis
Infarcts	Dystopia
Tumors	

C Affections of perinephric structures

Perinephritis	Retroperitoneal masses causing pressure on parenchyma
Tumors	Wilms tumor
Hematoma	

D Affections of ureter

Obstruction (pelvis, ureter prostate urethra)	Pyelitis

Cerebral

Increased intracranial pressure (trauma, tumor inflammation)	Anxiety states
Diencephalic stimulation	Lesions of brain stem (ascending paralysis, poliomyelitis)
	Acute porphyria

seems to have little correlation with age (see arteriosclerotic hyper tension p 39)

ARTERIAL PRESSURE IN THE THIGH

Comparatively little work has been done on measurement of arterial pressure in the thigh, yet this procedure is important, especially in the diagnosis of hypertension due to coarctation of the aorta In an important experimental study in dogs Hamilton and Dow showed by intra arterial optical measurement that peak systolic pressure and pulse pressure increase gradually from the aortic arch to the femoral artery although the mean pressure remains constant. In normal human subjects as measured by compression cuffs systolic pressure is constantly higher in the thigh than in the arm the difference commonly being from 20 to 40 mm. Hg This is due to the sum of the increased intra arterial systolic pressure and the increased pressure necessary to compress the large tissue mass Based on blood pressure measurements with a standard auscultatory technic (13 × 23 cm. cuff placed over the popliteal artery with the midportion of the cuff 10 cm. above the upper edge of the patella with subject prone) in 500 normal men aged 18–35 Wendkos and Rossman found the average systolic and diastolic pressures re spectively 36 and 21 mm Hg higher than in the arm The average arterial pressure in the thigh was thus 155/92 mm. Hg and in the arm 118/71 mm. Hg The Joint Committees recommend a 15 cm. cuff for measurements in the leg

CLASSIFICATION OF HYPERTENSION

It is becoming increasingly clear that arterial hypertension is caused by and associated with, a large number of diseases The association with Bright s disease and adrenal tumors has long been known but only recently has it been more generally appreciated that pyelonephritis pituitary basophilism, thymic tumors and a

course The greatest difficulty of such schemes is that the effort to simplify has often led to use of inadequate observational data A second difficulty lies in the failure to realize that the patients in one group may individually show wide variations in their course as unsuspected or intercurrent factors come into play The grouping of a patient which ends in the simple phrase she belongs to group D does not automatically brush away the variations and vagaries of individual courses and frequently if not always pretends to more than is actually known

Keith and Wagener s method of grading is undoubtedly one of the most useful available and has been widely employed. It should be stressed again and again that this is not an etiologic classification as is often implied The following tabulation shows the schema of grading proposed by them.

DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION
(Keith and Wagener)

Group 1 Retinal changes consist of mild narrowing or mild sclerosis of the arterioles. It is compatible with good health for many years. The blood pressure is not excessively high and falls during rest.

Group 2 The changes in the retinal vessels are more marked than in group 1 but retinitis is not present The disease is more progressive the blood pressure is higher and more sustained, but general health is good and cardiac and renal function satisfactory

Group 3 Angiospastic retinitis together with definite sclerotic changes in the arterioles occurs but edema of the disk is not presen The hypertension is high and sustained. Although cardiac and renal function may be adequate *sometimes* there are altera ions, as indicated by dyspnea on exertion, changes *in the* electrocardiogram and nocturia. Nervousness, headache vertigo and visual disturbances may occur Proteinuria and hematuria may be present.

Group 4 The important retinal alteration is edema of the disks. There is also marked spastic and organic narrowing of the arterioles with diffuse retinitis Characteristic symptoms are nervousness, asthenia, loss of weight headache visual disturbances, dyspnea on exertion and nocturia. Proteinuria, cylindruria and red blood cells are usually present Prognosis is serious.

Cardiovascular

Heart failure	Coarctation of aorta
Arteriovenous fistula	Polycythemia
Heart block	Atheromatosis

Endocrine

Pheochromocytoma	Pituitary basophilism (?)
Adrenal carcinoma	Acromegaly
Adrenal hyperplasia (?)	Thymic carcinoma
Chorionepithelioma	Hyperthyroidism
Adrenal like ovarian tumor	Arrhenoblastoma
Cushing s syndrome	Desoxycorticosterone

Unknown

Essential hypertension	Malignant hypertension

It is however an unpleasant truth that the patients with known or suspected causes for their hypertension constitute only a small percentage of those suffering from arterial hypertension At least 90–95 per cent have the essential or malignant variety

The classification of hypertension of known or suspected origin into endocrine cardiovascular renal and nervous categories has been taken over with varying degrees of assurance into the classification of essential and malignant hypertension In some cases the search for initiating factors in one or another of these areas has altered the diagnosis from that of essential hypertension Still with present day methods criteria are not yet available which place most patients with finality in one group or another In our experience patients with essential or malignant hypertension seem to have broadly similar patterns of disease more or less decisively modified from one patient to another by contributions from for example the endocrine glands or the nervous system A matter of importance then is to develop criteria and sufficient clinical acumen to analyze and evaluate these interlocking influences

Etiologic classification being in the strict sense impossible increasing attention is being given methods of classification of essential hypertension which evaluate the process in terms of severity and

course The greatest difficulty of such schemes is that the effort to simplify has often led to use of inadequate observational data A second difficulty lies in the failure to realize that the patients in one group may individually show wide variations in their course as unsuspected or intercurrent factors come into play The grouping of a patient which ends in the simple phrase she belongs to group D does not automatically brush away the variations and vagaries of individual courses and frequently if not always pretends to more than is actually known.

Keith and Wagener s method of grading is undoubtedly one of the most useful available and has been widely employed It should be stressed again and again that this is not an etiologic classification as is often implied The following tabulation shows the schema of grading proposed by them.

DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION
(Keith and Waeener)

Group 1 Retinal changes consist of mild narrowing or mild sclerosis of the arterioles. It is compatible with good health for many years. The blood pressure is not excessively high and falls during rest.

Group 2 The changes in the retinal vessels are more marked than in group 1 but retinitis is not present The disease is more progressive the blood pressure is higher and more sustained but general health is good and cardiac and renal function satisfactory

Group 3 Angiospastic retinitis together with definite sclerotic changes in the arterioles occurs but edema of the disk is not present The hypertension is high and sustained Although cardiac and renal function may be adequate sometimes there are alterations, as indicated by dyspnea on exertion changes in the electrocardiogram and nocturia. Nervousness, headache vertigo and visual disturbances may occur Proteinuria and hematuria may be present

Group 4 The important retinal alteration is edema of the disks. There is also marked spastic and organic narrowing of the arterioles with diffuse retinitis. Characteristic symptoms are nervousness, asthenia, loss of weight headache visual disturbances, dyspnea on exertion and nocturia Proteinuria, cylindruria and red blood cells are usually present. Prognosis is serious

COMMENT — *A grading scheme such as this has the distinct advantage of giving some notion of prognosis For example three years after the first examination 20 per cent of the patients in group 1, 36 per cent in group 2 75 per cent in group 3 and 94 per cent in group 4 were dead*

This method depends chiefly on the state of the eyegrounds, undoubtedly a wise choice It harks back to the experience of most clinicians namely, that if one had to make a choice among all the instruments of examination the ophthalmoscope would be most highly esteemed The grading obviously lacks precision, which has been sacrificed for simplicity

There is some question as to the validity of placing so much stress on the occurrence of papilledema It will be observed that groups 3 and 4 are divided by the presence or absence of this sign We believe that hemorrhage except in older people and severe hemorrhages and exudates at any age often are shortly followed by papilledema Thus when hemorrhages and exudates occur the prognosis is serious and it is only made a little more so by the appearance of papilledema But more penetrating observations are necessary before this point can be settled So *while ophthalmoscopic grading of severity has its usefulness physicians must guard against its inviting simplicity*

The classification of the phases of *essential hypertension that we propose is based on our interpretation of the natural history of the disease It is formed in such a way that* a term may be applied which will in a measure characterize all aspects of the disease which may be discovered during the examination Table 3 shows our grouping

TABLE 3 — CLASSIFICATION OF THE PHASES OF ESSENTIAL HYPERTENSION

A Prehypertension (p 60)

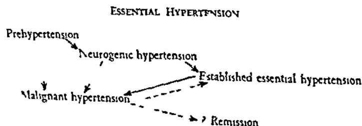
B Neurogenic hypertension (p 63)

C. Established essential hypertension (p 66)
  1 Vascular adaptation fully maintained (early hypertension)
  2 Vascular adaptation failing
    Progress
      Rapid (severe essential hypertension)
      Slow (mild or benign essential hypertension)
    Major site
      a) Cardiac (hypertensive heart disease)
      b) Cerebral
      c) Renal
      d) Other

D Malignant hypertension (malignant syndrome) (p 71)

Until recently the physician has been confronted more with the problems of established essential and malignant hypertension than with the other phases which until the advent of routine physical examinations have been largely overlooked It is our impression that the most common progression of the disease is from prehypertension through neurogenic hypertension to established essential hypertension with subsequent failure of vascular adaptation and in some patients the superimposition of the syndrome of malignant hypertension But this progression is not inevitable The disease may persist or even seem to appear suddenly in any one of its phases

Omitting the subgroups the stages of the disease may be schematized in the following manner in which the solid arrows represent the common and the dotted ones the less frequent trends



COMMENT—A grading scheme such as this has the distinct advantage of giving some notion of prognosis For example three years after the first examination 20 per cent of the patients in group 1 36 per cent in group 2, 75 per cent in group 3 and 94 per cent in group 4 were dead

This method depends chiefly on the state of the eyegrounds, undoubtedly a wise choice It harks back to the experience of most clinicians namely that if one had to make a choice among all the instruments of examination, the ophthalmoscope would be most highly esteemed The grading obviously lacks precision which has been sacrificed for simplicity

There is some question as to the validity of placing so much stress on the occurrence of papilledema It will be observed that groups 3 and 4 are divided by the presence or absence of this sign We believe that hemorrhage, except in older people, and severe hemorrhages and exudates at any age often are shortly followed by papilledema Thus when hemorrhages and exudates occur, the prognosis is serious and it is only made a little more so by the appearance of papilledema But more penetrating observations are necessary before this point can be settled So while ophthalmoscopic grading of severity has its usefulness physicians must guard against its inviting simplicity

The classification of the phases of essential hypertension that we propose is based on our interpretation of the natural history of the disease It is formed in such a way that a term may be applied which will in a measure characterize all aspects of the disease which may be discovered during the examination Table 3 shows our grouping

TABLE 3—CLASSIFICATION OF THE PHASES OF ESSENTIAL HYPERTENSION

A Prehypertension (p 60)

B Neurogenic hypertension (p 63)

2 Hypertension of Known or Attributable Origin

THE CLASSIFICATION of arterial hypertension we have proposed (p 25) deals with five categories of disease in four of which the nature of the ailment is either known or suspected. Essential hypertension, the remaining category is a disease of unknown origin Into it enter constitutional psychologic and pathophysiologic factors none of which can be defined with precision This disease forms the subject matter of this book Hypertension of known origin does not. But since the diagnosis of essential hypertension depends on exclusion of these other less common forms of arterial hypertension this field too must pass in brief review

I RENAL HYPERTENSION

Glomerulonephritis—Arterial hypertension systolic and diastolic is almost a constant finding at some time in the course of acute and chronic glomerulonephritis In acute nephritis the onset of hypertension is often abrupt and severe with a tendency toward acute left ventricular failure There are generalized edema pallor proteinuria hematuria and cylindruria. The renal functional pattern is essentially one of decreased glomerular filtration with a low filtration fraction (p 279) and decrease in the rate of glo-

BIBLIOGRAPHY

ALLEN E V in Stroud W D The Diagnosis and Treatment of Cardiovascular Disease (Philadelphia F A Davis Company 1940) Vol. I p 1320

AYMAN D AND GOLDSHINE A D Blood pressure determinations by patients with essential hypertension I The difference between clinic and home readings before treatment Am J M Sc 200 465 1940

CURRENS J H A comparison of the blood pressure in the lying and standing positions A comparison of 500 men and 400 women Am Heart J 35 646 1948

KEITH N M WAGENER H P AND BARKER N W Some different types of essential hypertension Their course and progress Am J M Sc 197 332 1939

PAGE I H Classification of hypertension J Indiana M A 32 562 1939

ROBINSON S C Hypotension The ideal normal blood pressure New England J Med 223 407 1940

——— AND BRUCER M Range of normal blood pressure A statistical and clinical study of 11 383 persons Arch Int Med 64 409 1939

ROTH G M MCDONALD J B AND SHEARD C The effect of smoking cigarettes and of intravenous administration of nicotine on electrocardiogram basal metabolic rate cutaneous temperature blood pressure and pulse rate of normal persons J A M A 125 761 1944

SCHROEDER H A AND STEELE J M Studies on essential hypertension I Classification Arch Int Med 64 927 1939

TRELOAR A Normal blood pressure Arch Int Med 66 848 1940

WENDKOS M H AND ROSSMAN P L The normal blood pressure in the lower extremity Am Heart J 26 623 1943

tration As the terminal phase is approached tubular secretory capacity diminishes rapidly and to levels well below those seen in malignant hypertension Differentiation from the latter condition is aided by studies of renal function and by demonstration of comparatively mild degrees of extrarenal cardiovascular damage to heart and brain. The differentiation is significant for malignant hypertension progresses rapidly from the stage of impending uremia to death whereas chronic glomerulonephritis may with proper care remit or stabilize at this level for long periods

The general pattern of intercapillary glomerulosclerosis associated with diabetes is similar to that of chronic glomerulonephritis

Pyelonephritis —Pyelonephritis is the most common renal disease if we except renal injury due to arterio- and arteriolosclerosis Raaschou found pyelonephritis in 5 6 per cent of autopsies in a general hospital and showed that it accounted for 58 per cent of the deaths in uremia No anatomic contributory cause of the infection could be found in one third of the cases The problem is therefore not exclusively urologic but one of important general interest in a condition which is too often unrecognized

What is its relation to hypertension? Most arterial hypertension is at the outset at least not of renal origin The incidence of hypertension in patients with pyelonephritis or with genitourinary disease is not greater than in control groups But is it logical to conclude that pyelonephritis has nothing to do with hypertension while admitting that glomerulonephritis does and while acknowledging the establishment of perinephritis as an eminently satisfactory means of producing experimental hypertension? Or is it better to jump in the other direction and conclude as some have that chronic pyelonephritis is the most important genetic factor in the syndrome of malignant hypertension? Actually the truth lies between the means of these opposing views

For example it should be recognized that infection alone can mask the presence of mild hypertension so that groupings of blood

merular filtration per unit of secretory capacity The defect in filtration accounts in part for edema sodium retention and symptoms of left heart failure Decreased filtration is attributable largely to lesions of the glomerular capillaries and to renal interstitial edema and exudation, the extent to which spasm of arterioles participates is unknown Instances in which hypertension and oliguria have been relieved by high caudal anesthesia suggest that vasomotor spasm may be a factor in the renal functional pattern There may be a neurogenic factor in the peripheral vasospasm also Spasm commonly segmental can be seen in the retinal arterioles, although these are sometimes obscured by edema Sedimentation rate is increased Fever, if present, is slight A history of recent upper respiratory or cutaneous infection can usually be elicited Diagnosis is not usually difficult Treatment during the oliguria is based on limiting *fluid and salt to the absolute needs of replacement and on careful* digitalization should signs of cardiac failure appear Magnesium *sulfate is used to relieve encephalopathy and in crises of left heart* failure, oliguria or encephalopathy high caudal or spinal anesthesia has been recommended In general the treatment of acute nephritis is similar to that of eclamptogenic toxemia of pregnancy, which process it resembles in many particulars

The nephrotic phase of chronic glomerulonephritis is characterized by edema and massive proteinuria Hypertension is often absent and is seldom severe However as glomerulonephritis advances edema recedes renal function deteriorates and the blood pressure usually rises There are anemia weakness and fatigability Urinary losses of sodium and potassium may become excessive The retinal vessels show constriction and sclerosis With the approach of uremia or the advance of anemia exudates appear in the eye grounds and are followed by hemorrhages The exudates are commonly more extensive and the hemorrhages deeper and less sharp in outline than those of malignant hypertension The renal functional pattern is one of predominant reduction of glomerular fil

and the family history Hypertension especially when severe and when it appears in persons under 45 who definitely do not have a family history of hypertension puts the probabilities about 3 1 in favor of renal origin

The treatment of bilateral pyelonephritis begins with a search for urologic defects When these are irremediable or not demonstrable the next step is to sterilize the urinary tract. In so doing treatment from its outset should be aimed at the immediate and total eradication of all bacteria in the kidney tissues Antibacterials and antibiotics should therefore be used in full dose The choice of drug should, when possible be made by cultural selection of the agent to which the organism is most susceptible Half measures and inadequate treatment are worse than useless since they merely create resistant strains of organisms The agent chosen whether a sulfonamide or an antibiotic should be given in full therapeutic dosage from the outset. It is an expensive and sometimes a dangerous error to continue treatment for too long a time Persistence of a positive urine culture under treatment indicates either an inappropriate choice of drug or the development of resistance in the organism The so-called urinary antiseptics should not be relied on in this dangerous disease

Unilateral renal disease—Pyelonephritis constitutes a large proportion of unilateral renal lesions Their association with hypertension is analogous to that of pyelonephritis in that compilations of cases do not demonstrate an undue incidence of hypertension whereas reports of individual cases establish a close association How close this association is remains unknown except in patients in whom unilateral nephrectomy results in cure of established hypertensive disease A stringent review by Homer Smith of the available data indicates a cure rate of about 20 per cent which is indisputably greater than the frequency of spontaneous remission in essential hypertension Until the elusive factors which initiate and perpetuate renal hypertension are better understood the approach

pressures of pyelonephritis may not have the significance they at first suggest Further, deference must be paid to the excellent clinical and experimental proofs that renal injury, including that associated with pyelonephritis is sometimes the cause of arterial hypertension Examples, suitably chosen and carefully documented are more important than rules In brief arterial hypertension and chronic pyelonephritis are both common ailments The tendency in recent years has been in the direction of indiscriminately labeling the one as effect and the other as cause This is inadmissible But the fact remains that the association of pyelonephritis with severe hypertension exists The relationship is uncommon but cannot be safely ignored

Diagnosis of chronic pyelonephritis is not easy It begins with a review of the history back into childhood for evidences of urinary infection The first evidences may be extraurinary and consist of fatigability loss of weight and appetite and anemia Proteinuria is rarely very severe The urinary sediment should be repeatedly and deliberately searched for red and white blood cells and for tubular epithelium all of which may be absent in some of the examinations Costolumbar or costovertebral tenderness is suggestive evidence Both are often absent Urine cultures positive for a pathogenic organism on two occasions or preferably more go far toward making the diagnosis It is completed by a more searching study of renal function and structure This includes the tests of renal function intravenous urography and cystoscopy with bilateral measurement of the excretion time of indigo carmine or phenol red of urinary urea concentrations and examinations of the urine sediments for cells casts and bacteria

If hypertension is present the problem of relating it to the renal disease depends on an estimate of probabilities Time relationships between the onset of the pyelonephritis and the appearance of hypertension are important but often cannot be established Platt has suggested two important clinical guides the patient's age

and the family history Hypertension especially when severe and when it appears in persons under 45 who definitely do not have a family history of hypertension puts the probabilities about 3 1 in favor of renal origin

The treatment of bilateral pyelonephritis begins with a search for urologic defects When these are irremediable or not demonstrable the next step is to sterilize the urinary tract. In so doing treatment from its outset should be aimed at the *immediate* and *total* eradication of all bacteria in the kidney tissues Antibacterials and antibiotics should therefore be used in full dose The choice of drug should when possible be made by cultural selection of the agent to which the organism is most susceptible Half measures and inadequate treatment are worse than useless since they *merely create* resistant strains of organisms The agent chosen whether a sulfonamide or an antibiotic should be *given in full* therapeutic dosage *from* the outset. It is an expensive and sometimes a dangerous error to continue treatment for too long a time Persistence of a positive urine culture under treatment indicates either an inappropriate choice of drug or the development of resistance in the organism. The so-called urinary antiseptics should not be relied on in this dangerous disease

Unilateral renal disease —Pyelonephritis constitutes a large proportion of unilateral renal lesions Their association with hypertension is analogous to that of pyelonephritis in that compilations of cases do not demonstrate an undue incidence of hypertension whereas reports of individual cases establish a close association How close this association is remains unknown except in patients in whom unilateral nephrectomy results in cure of established hypertensive disease A stringent review by Homer Smith of the available data indicates a cure rate of about 20 per cent which is indisputably greater than the frequency of spontaneous remission in essential hypertension Until the elusive factors which initiate and perpetuate renal hypertension are better understood the approach

to the problem of hypertension due to unilateral renal disease will continue to be empiric

It is interesting to note that the concept of unilateral renal disease as a cause of severe hypertension was based on clinical observations which antedate the production of satisfactory experimental renal hypertension One of the earliest and most complete descriptions is that by Ask Upmark who described a syndrome of unilateral renal hypoplasia with deformity and recession of the renal pelvis sometimes associated with other congenital defects and more common in females, which gives rise to the syndrome of malignant hypertension, usually during the adolescent period of rapid growth

In a study (Ratliff *et al*) of 49 such patients 17 had no symptoms of disease of the urinary tract, 19 had unilateral chronic pyelonephritis which in eight was associated with renal hypoplasia Eleven showed hydronephrosis and four tuberculosis Relief of hypertension followed nephrectomy in 17 (35 per cent) In the whole group of hypertensive patients from which these 49 were drawn by routine urologic survey about 5 per cent showed urinary abnormalities half of which were amenable to nephrectomy Thus the probability of successful treatment based on careful routine urologic study of hypertensive patients lies between 1 in 100 and 1 in 200

Expense is a large factor when the odds are so heavily against the patient s obtaining relief from urologic examinations Patients must therefore be screened in some way before entering on a full urinary survey The simplest and cheapest as well as the most effective methods for such selection are intravenous urography and study of the urinary sediment and culture When these indicate the presence of unilateral renal disease a more searching study is clearly in order And when definite evidence of unilateral renal disease has been obtained the probability of a renal origin of the associated hypertension must still be estimated from Platt s criteria of age

severity of hypertension and absence of a family history of the disease Thus in the older patient with mild hypertension a positive family history a normal excretory urogram and sterile urine no further study is indicated. But in young people with severe disease the search for urinary abnormalities should be continued even when the intravenous urogram is normal and the urine sterile

Once it is established that there is unilateral renal disease and that this is probably a cause of hypertension the problem is whether or not to advise nephrectomy This operation is indicated on surgical grounds in about a third of the cases and this without reference to the continuance of the hypertension In the other two-thirds the decision is based on the probability of relieving the hypertensive disease

In this connection an important principle is derived from animal experiments Nephrectomy of the offending kidney in dogs with experimental renal hypertension causes prompt remission of arterial pressure even when the tension has been high over long periods In contrast nephrectomy in hypertensive rats is less and less effective in reducing the pressure as the duration of the hypertension is prolonged. A study of the normal kidney of persistently hypertensive uninephrectomized rats demonstrated to Wilson and Byrom the presence of renal vascular disease This observation led them to the concept of a vicious cycle in renal hypertension the abnormal kidney causes hypertension hypertension when prolonged results in arterial and arteriolar disease renal arterial disease begins in the contralateral normal kidney causes pressor endocrine activity and thus increases arterial pressure further or after nephrectomy causes hypertension to persist. The evidence for this concept has not compelled full agreement among investigators Still it has much to commend it particularly since clinical experience suggests that in this respect, as perhaps in others man resembles more his enemy the rat than his friend the dog

It is an application of this principle that age and duration of

hypertension are important factors in the selection of patients for nephrectomy Age enters into the pattern for two reasons One is that hypertension after age 45 is much more probably essential than renal, the other is the fact that sclerosis and arterial disease seem to proceed more rapidly in old vessels so that even when a renal origin can be established it is unlikely that nephrectomy will be of much avail Duration of hypertension is merely an index of the probability of contralateral renal arterial disease The decision is sometimes based on rules of thumb which would deny operation after two, three or four years of established hypertension However arterial disease rather than age or duration is the true limiting factor We recall one woman—an exceptional case to be sure—who at 32 had had *hypertension for 16 years as the result of healed* unilateral renal tuberculosis Nephrectomy by Dr Charles Higgins resulted in a cure which has persisted for four years The decision to operate was made despite the duration of the hypertension because she showed no evidences of loss of vascular adaptation to hypertension in the retinal vessels heart and aorta or contralateral kidney

No simple rule will guarantee a good result from nephrectomy A positive family history doubt as to the presence of disease in the *other kidney long duration of hypertension age over 45 and presence* of arterial and arteriolar sclerosis contraindicate a nephrectomy which is being considered on medical grounds Positive indications are less obvious They include severe hypertension of recent origin in young people whose renal disease is definitely unilateral whose other kidney is hypertrophied and who do not show any evidences of vascular senescence In this connection it is important that the acute destructive lesions of retinopathy in the malignant syndrome *are not interpreted as due to arteriolar sclerosis* and as contraindications

In summary the careful search for patients who can be relieved by operation is worth while *After all* a cure rate of even *1 in 200* is an achievement in unselected cases of severe hypertension and in

properly selected cases a rate of 1 in 5 or better can be expected The fabulous claims of enthusiasts of the early 1940s have been countered by the searching analyses of the more pessimistic and as balance has been reached nephrectomy has come to assume its proper perspective in treatment

II HYPERTENSION OF CARDIOVASCULAR ORIGIN

Arteriosclerotic hypertension—Arteriosclerotic hypertension consists in an increase of arterial pressure predominately and some times exclusively of systolic pressure which is due to loss of elasticity of the aorta Its mechanism is discussed elsewhere (p 124) Briefly stated failure of the elastic arteries to stretch to accommodate the thrust of blood during systole causes the systolic pressure to rise Since the run-off of blood in diastole is not usually checked by any considerable increase in peripheral resistance as it is in essential hypertension diastolic pressure may be normal or even decreased In some patients the condition occurs in a mixed form in association with increased peripheral resistance and mild essential hypertension

Typically the condition has its onset in men at about age 50 and in women about a decade later It does not of itself cause symptoms However since it is evidence of arterial senescence it is associated with increased incidences of coronary artery disease in women and of renal arteriosclerosis and cerebral accidents in both sexes These complications are less common than they are in the mixed form of systolic diastolic arteriosclerotic plus essential hypertension (Zeman and Schwartz) and in essential hypertension In fact were it not for its slow progress toward cerebral or renal failure and occasional abrupt complications the condition might be regarded as benign It does little to cut short the biblical term of life

It is most often and most unnecessarily complicated by the

hypertension are important factors in the selection of patients for nephrectomy Age enters into the pattern for two reasons One is that hypertension after age 45 is much more probably essential than renal, the other is the fact that sclerosis and arterial disease seem to proceed more rapidly in old vessels, so that even when a renal origin can be established it is unlikely that nephrectomy will be of much avail Duration of hypertension is merely an index of the probability of contralateral renal arterial disease The decision is sometimes based on rules of thumb which would deny operation after two three or four years of established hypertension However, arterial disease rather than age or duration is the true limiting factor We recall one woman—an exceptional case to be sure—who at 32 had had hypertension for 16 years as the result of healed unilateral renal tuberculosis Nephrectomy by Dr Charles Higgins resulted in a cure which has persisted for four years The decision to operate was made despite the duration of the hypertension because she showed no evidences of loss of vascular adaptation to hypertension in the retinal vessels heart and aorta or contralateral kidney

No simple rule will guarantee a good result from nephrectomy A positive family history doubt as to the presence of disease in the other kidney long duration of hypertension age over 45 and presence of arterial and arteriolar sclerosis contraindicate a nephrectomy which is being considered on medical grounds Positive indications are less obvious They include severe hypertension of recent origin in young people whose renal disease is definitely unilateral whose other kidney is hypertrophied and who do not show any evidences *of vascular senescence In this connection it is important* that the acute destructive lesions of retinopathy in the malignant syndrome are not interpreted as due to arteriolar sclerosis and as contraindications

In summary the careful search for patients who can be relieved by operation is worth while After all a cure rate of even 1 in 200 is an achievement in unselected cases of severe hypertension and in

The infantile type of coarctation commonly involves the whole isthmus of the aorta rather than a small segment, as in the adult type It is much the more serious and its victims seldom live more than a few hours or days after birth The adult type with which we are concerned here consists of constriction of varying degrees at, or more commonly just below the insertion of the ductus arteriosus or its obliterated remnant the ligamentum arteriosum. It is compatible with life for many years When the narrowing is severe and collateral circulation not wholly adequate patients seldom live longer than 20–30 years Obviously the difficulty in prognosis is to decide how adequate is the collateral circulation.

The mechanism by which the hypertension is produced is not clear Narrowing of the aorta obviously increases resistance to the flow of blood But there is added to this a generalized increase in peripheral resistance Thus Steele showed that the *diastolic* pressure below the narrowed area of the aorta is also elevated above normal

Death from coarctation is usually due in decreasing frequency to (1) congestive heart failure (2) rupture of the aorta or heart (3) cerebral hemorrhage or (4) bacterial endocarditis The signs and symptoms of the anomaly especially if it is mild are not characteristic and it is not unusual for it to be discovered only at necropsy But when the narrowing is of sufficient magnitude many pathognomonic signs appear First, systolic and diastolic hypertension appear in the upper part of the body and often diastolic but not systolic hypertension in the lower part. The femoral pulses are delayed and diminished. The changes need not be great and indeed the diagnosis is often missed because they are not. The pulse wave contours below the coarctation are flat smooth and somewhat delayed Second there is development of collateral circulation involving chiefly the internal mammary intercostal scapular and deep epigastric arteries The first three of these vessel systems become dilated often hypertrophied, and may be seen and felt. The we

physician who mistakes this form of hypertensive disease for true essential hypertension He thus creates an *iatrogenic hypertensive neurosis which will shadow the patient s declining years and perhaps lead him into a dreary round of diets drugs doctors and worse True, the aorta may be dilated and tortuous the fundal arterioles sclerotic* and the patient s cardiac and renal functions below normal standards for adult healthy people But since the disease is relatively benign and since the age in which it occurs is ordinarily one of decreasing vigor and accomplishment none of this is very alarming In particular the physician should recognize the fact that the mechanism of this hypertension (a positive disproportion between cardiac output and aortic elasticity) is such that the pressure levels fluctuate widely This fact paradoxical as it may seem that a hypertension due to increased rigidity of vessel walls should be so fluctuant accounts for many mistaken and now forgotten claims of therapeutic success It also points the way to treatment

Treatment is directed at stabilizing at a relatively low level the rate of cardiac output *It is accomplished by rest in bed rest periods during the day mild sedation reduction of excess weight (without pressor amines) and all the general measures of wider interests, restful diversions and philosophic integration which result in a comfortable and happy old age Treatment is difficult in patients whose aortic flesh is weak while the spirit is still strong and youthful In* some of these it is perhaps unfortunate that arterial pressure was measured and a diagnosis of hypertension ever made *Still it is only* a matter of logic and good hygiene that these too should let up a bit from the drive of life and in so doing protect their aging vessels from undue strains

Coarctation of the aorta—It is important to differentiate coarctation of the aorta from essential and malignant hypertension because the prognosis is often very different and especially because surgical relief of coarctation is usually obtainable

The optimal ages for performance of the operation appear to be from 6 to 20 years Beyond 25 arteriosclerotic changes in the aorta may make it subject to rupture and unsuitable for anastomosis After successful operation hypertension may be completely relieved and signs and symptoms of congestive failure clear

III HYPERTENSION OF ENDOCRINE ORIGIN

The adrenal cortex Cushing s syndrome and Cushing s disease —The term Cushing s syndrome is applied whether the characteristic syndrome is of adrenal or pituitary origin The term Cushing s disease is restricted to cases of basophilic tumor of the pituitary The clinical features of Cushing s syndrome listed by Albright are (*a*) insulin resistant, rather mild diabetes (*b*) muscular weakness (*c*) osteoporosis especially of the spine (*d*) a thin skin marked by striae easily bruised and susceptible to infection (*e*) impotence and amenorrhea (*f*) moderate obesity most marked in the face (*g*) mild hirsutism (*h*) mild erythrocytosis and (*i*) hypertension The hypertension is often associated with relatively severe nephrosclerosis (Table 4) The association of hypertension and arteriovascular disease with this condition results in the consideration here of a condition which although uncommon is so dramatic as to be familiar to most clinicians

The disease has further interest because it is one of Nature s experiments in endocrine physiology The basic pathology varies it may be a cancer or adenoma of one adrenal cortex sometimes of both it may be a basophil adenoma of the pituitary in which case it is usually associated with bilateral hyperplasia of the adrenal cortices the cortices may be hyperplastic without other lesions or in some patients no causal adrenal or pituitary lesion can be satisfactorily demonstrated

The pathologic physiology is much more uniform and consists essentially in hypercorticoidism The excessive production of the

known notching or scalloping of the posterolateral inferior aspects of the ribs seen on x ray is due to erosion by the enlarged inter costal vessels Third, the heart enlarges with evidences of failure acute or chronic along with prolonged systolic murmurs heard over the aortic area transmitted to the back and often along the col lateral circulation The normal roentgen shadow of the cardiac knob is decreased or absent The ascending aorta may be moderately dilated and appears to rise higher than normal in the neck

Diagnosis may be finally established by an arteriogram For this purpose, 70 per cent diodrast* is injected intravenously and after a suitable time to allow circulation through heart and lungs the picture is taken Campbell and Suzman describe a maneuver which *may be useful in the diagnosis of coarctation The patient stoops or* bends forward with the arms hanging at the sides Collateral arteries under the skin of the back and sides of the chest appear *where none were visible before They believe this sign due to* widening of the costoclavicular space and hence it follows that in the usual positions the space between the clavicle and the first rib is sufficiently narrow to produce some constriction of the subclavian artery In patients with coarctation who do not show the sign the space is wide enough not to compress even the dilated subclavian artery

The outlook for patients with adult coarctation has undergone radical change with development of surgical operations for correc tion of the anomaly chiefly by Crafoord and Nylin Gross and Blalock The usual operation consists of freeing the aorta and the narrowed segment removal of the anomaly and anastomosis of the cut ends of the aorta The operative mortality has not been unduly great considering the seriousness of the problem Not all patients are suitable candidates because of the extent of the anomaly and the length and elastic quality of the vessel but enough in the younger age groups have the chance of success to justify surgical exploration

The optimal ages for performance of the operation appear to be from 6 to 20 years Beyond 25 arteriosclerotic changes in the aorta may make it subject to rupture and unsuitable for anastomosis After successful operation hypertension may be completely relieved and signs and symptoms of congestive failure clear

III HYPERTENSION OF ENDOCRINE ORIGIN

The adrenal cortex Cushing s syndrome and Cushing s disease —The term Cushing s syndrome is applied whether the characteristic syndrome is of adrenal or pituitary origin The term Cushing s disease is restricted to cases of basophilic tumor of the pituitary The clinical features of Cushing s syndrome listed by Albright are (*a*) insulin resistant rather mild diabetes (*b*) muscular weakness (*c*) osteoporosis especially of the spine (*d*) a thin skin marked by striae easily bruised and susceptible to infection (*e*) impotence and amenorrhea (*f*) moderate obesity most marked in the face (*g*) mild hirsutism (*h*) mild erythrocytosis and (*i*) hypertension The hypertension is often associated with relatively severe nephrosclerosis (Table 4) The association of hypertension and arteriovascular disease with this condition results in the consideration here of a condition which although uncommon is so dramatic as to be familiar to most clinicians

The disease has further interest because it is one of Nature s experiments in endocrine physiology The basic pathology varies it may be a cancer or adenoma of one adrenal cortex sometimes of both it may be a basophil adenoma of the pituitary in which case it is usually associated with bilateral hyperplasia of the adrenal cortices the cortices may be hyperplastic without other lesions or in some patients no causal adrenal or pituitary lesion can be satisfactorily demonstrated

The pathologic physiology is much more uniform and consists essentially in hypercorticoidism The excessive production of the

gluconeogenic adrenal steroids is believed to account for the diabetes *muscular* weakness, osteoporosis and loss of skin tissue The mechanism of the hypertension is not as obvious except as it has its counterpart in the experimental hormonal (desoxycorticosterone) hypertension of rats (Selye) This association and the fact that adrenal cortex function is in some way essential to the maintenance of experimental renal hypertension may have a wider relevance to the problem of clinical essential hypertension

Indeed, excessive dosage of desoxycorticosterone causes a sharp

TABLE 4—RENAL FUNCTION IN CUSHING S SYNDROME

	PATIENT NUMBER				
	1	2	3	4	5
Renal blood flow*	687	495	518	446	463
Renal plasma flow*	374	271	295	201	278
Glomerular filtration rate*	77	77+	71	71+	59+
Tm_{D-1} mg	39 9	32 2+	27 8+	26 7+	19 6+
Arterial pressure (Pm)		135	120	140	122
Filtration fraction	0 21	0 28	0 24	0 35	0 21
Renal blood flow/$Tm_{D\ I}$	17 2	15 4	18 6	16 7	23 6
Glomerular filtration rate/$Tm_{D\ I}$	1 92	2 38	2 54	2 66	3 0
Resistance					
Afferent		3 78	2 05	2 82	2 49
Efferent		1 42	1 24	1 95	0 64
Total		5 20	3 33	4 77	3 12

In cc /1 73 sq m /m n

increase in arterial pressure in some patients with Addison s disease and in normal subjects as well as in hypertensive patients What appears to be malignant hypertension has thus been induced in a few patients with Addison s disease

Selye and co workers have shown that administration of large doses of desoxycorticosterone acetate to rats results in nephrosclerosis hypertension and generalized severe arterial disease resembling panarteritis The experimental disease is more readily established in uninephrectomized animals which are given 1 per cent sodium chloride in their drinking water This fact which has been confirmed and extended in detail by Masson in our laboratory is

related by Selye to a general concept of the diseases of adaptation. It depends in part on the fact that administration of a suspension of lyophilized anterior pituitary to rats fed high protein diets also results in renal and arterial disease with some hypertension In outline it is proposed that insults to the bodily economy result in adaptive sequences of pituitary and adrenal activity With repeated or sustained stresses the mechanism of adaptation sticks as it were in high gear in the phase of resistance with excess adrenal activity and an outpouring of the desoxycorticosterone like mineralocorticoids i e adrenal cortical hormones which act predominately on electrolyte (Na, K) metabolism. These like desoxycorticosterone are presumed to act in causing renal and extrarenal vascular disease and hypertension eliciting and potentiating also the activity of the renal pressor system The advantages for research of such a broad conceptual outline are obvious If proof in detail of a wide spread or even more localized clinical application is lacking there is still much in the concept which bears on the general problem of hypertensive disease and most obviously on the cardiovascular aspects of Cushing s syndrome

Diagnosis is made from the summation of clinical features particularly of the first three noted above It may be confirmed in most cases by demonstration of high levels of urinary and plasma corticoids and of a negative nitrogen balance Some patients most commonly those with adrenal tumors show high levels of urinary 17 ketosteroids The further diagnosis between adrenal and pituitary and between tumor and hyperplasia is usually a matter of great difficulty

Treatment is also unsatisfactory The pathophysiology of the disease is an indication for administration of testosterone This has the aim of increasing protein anabolism so as to retard the katabolic activity of the excess corticoids Selye s experiments suggest that it might be advisable to u e a low sodium diet and in cases of pituitary origin a diet low in proteins Tumors of the adrenals

should be sought for and eradicated with *special precautions against* postoperative hypocorticoidism due to compensatory atrophy of the residual adrenal tissue Bilateral hemiadrenalectomy has been *done in a few patients with beneficial results In considering* operation one should remember that the katabolic aspect of the disease causes deficient wound healing with resultant increase in postoperative morbidity and mortality

The adrenal medulla Pheochromocytoma—Functioning tumors of the pheochrome adrenal medullary tissue, of extra adrenal medullary rests or of the organ of Zuckerkandl occur rarely Still, the increasing number of cases diagnosed and successfully treated indicate that the condition is more common than is generally thought Further since they are the cause of one of the few wholly remediable forms of hypertension they should always be borne in mind

These tumors are usually adenomas A few most of them apparently nonfunctioning are carcinomas About 10 per cent are bilateral The pathologic physiology consists essentially in hyperadrenalinemia and from recent studies probably hyper nor adrenalism which causes fluctuant episodic and hyperreactive *hypertension palpitation headaches hyperhidrosis anxiety* and tremor Some episodes terminate in diaphoresis and vascular collapse They are precipitated by movement compression of the *abdomen exposure to cold or emotion and are sometimes spontaneous* The attacks are associated with hyperglycemia sometimes with glycosuria and with hypermetabolism Some patients show increased *levels of glomerular filtration rate and urea clearance*

Continuous hypertension due to pheochromocytoma is less common than the intermittent form The findings in these cases may seem identical with those of severe *essential hypertension* The frequent presence of retinal hemorrhages and exudates may lead to the diagnosis of malignant hypertension Because of this similarity unsuspected adrenal medullary tumors have been *found in* about

1 in 200 patients during sympathectomy for essential hypertension Cahill has observed the change from remittent to sustained hyper tension in some cases

The mechanism of sustained hypertension is not as obvious as that of the intermittent type which is explicable as the result of hyperadrenalinemia alone However it has recently been shown that the normal adrenal and at least some pheochromocytomas con tain in addition to adrenaline nor adrenaline This compound is believed to be identical with sympathin E (excitatory sympathin) It differs from adrenaline in that its effects on the vascular tree are much closer to the hemodynamic changes of essential hypertension than are those of adrenaline Unlike adrenaline its pressor effect is not easily reversed by dibenamine * Consequently the suggestion has been made not only that nor adrenaline may participate in episodic crises but that its continuous secretion would account for sustained hypertension A further possible mechanism of sustained hypertension lies in the fact, demonstrated by Vogt and confirmed by us that perhaps via pituitary liberation of adrenocorticotrophin adrenaline precipitates liberation of excess adrenal cortical hormone Since as discussed in the preceding section hypercorticoidism is a cause of hypertension and vascular disease as well as of diabetes mellitus the adrenal cortex may participate in some of the mani festations of medullary tumors

The possibility of pheochromocytoma should be suspected when hypertension insulin resistant diabetes and hypermetabolism coin cide especially in young people and in children The condition is more common in females In patients with typical episodic crises the diagnosis can all but be established on clinical grounds Psycho neurosis (neurocirculatory asthenia) hyperthyroidism and the hy pertensive diencephalic syndrome (p 64) should be thought of in differential diagnosis The diagnostic tests which confirm or negate clinical impressions are listed in Table 5

The safest and probably the most specific of these tests is that

should be sought for and eradicated with special precautions against postoperative hypocorticoidism due to compensatory atrophy of the residual adrenal tissue Bilateral hemiadrenalectomy has been done in a few patients with beneficial results In considering operation, one should remember that the katabolic aspect of the disease causes deficient wound healing with resultant increase in postoperative morbidity and mortality

The adrenal medulla Pheochromocytoma—Functioning tumors of the pheochrome adrenal medullary tissue, of extra adrenal medullary rests or of the organ of Zuckerkandl occur rarely Still the increasing number of cases diagnosed and successfully treated indicate that the condition is more common than is generally thought Further since they are the cause of one of the few wholly remediable forms of hypertension they should always be borne in mind

These tumors are usually adenomas A few most of them apparently nonfunctioning are carcinomas About 10 per cent are bilateral The pathologic physiology consists essentially in hyperadrenalinemia and from recent studies probably hyper nor adrenalism which causes fluctuant episodic and hyperreactive hypertension palpitation headaches hyperhidrosis anxiety and tremor Some episodes terminate in diaphoresis and vascular collapse They are precipitated by movement compression of the abdomen exposure to cold or emotion and are sometimes spontaneous The attacks are associated with hyperglycemia sometimes with glycosuria and with hypermetabolism Some patients show increased levels of glomerular filtration rate and urea clearance

Continuous hypertension due to pheochromocytoma is less common than the intermittent form The findings in these cases may seem identical with those of severe essential hypertension The frequent presence of retinal hemorrhages and exudates may lead to the diagnosis of malignant hypertension Because of this similarity unsuspected adrenal medullary tumors have been found in about

indication for re-exploration In any event every patient should be tested for responses to the drugs listed before and again after operation. Surgery is complicated by difficulty in localizing the tumor and by pressor rises followed by vascular collapse during the operation. As a result, operative mortality has been high although improvements in surgical technic have decreased it in recent years Localization of the tumor is done by air insufflation roentgenograms when as is usual palpation and pyelography give no clue A transabdominal operation which allows visualization of both adrenals is preferable to a lumbar incision Excessive rises in pressure can be controlled with benzodioxane The sharp drop in pressure which follows removal of the tumor should be countered by intravenous infusion of arterenol[a] or epinephrine This field of surgery demands special skill and experience

Menopausal hypertension (p 77)

IV HYPERTENSION OF NERVOUS ORIGIN

Acute porphyria—As an example of hypertension of nervous origin acute porphyria serves admirably It is a familial disease characterized by the excretion in the urine of large amounts of porphyrins due to abnormality of pigment metabolism The pathologic changes are found chiefly in the nervous system and consist of degeneration of peripheral nerves sympathetic ganglions anterior and posterior horn cells Purkinje cells of the cerebellum and the cortical cells of the cerebrum

The clinical signs and symptoms are protean and may be divided roughly into four groups (1) Mental The patient appears to suffer from conversion hysteria If organic brain disease has already occurred the psychoneurotic behavior may be masked Between attacks the patient's mental state may be quite normal (2) Nervous with peripheral neuritis and ascending myelitis of the Landry type loss of motor power and paralyses usually incom

with benzodioxane A positive response consists in a reduction of arterial pressure to normal levels The value of the test is limited because not all patients show hypertension at the time of the test The customary dosage is 10 mg per square meter of body surface and the typical response in essential hypertension is a slight rise in arterial pressure Tetraethylammonium is also advocated because of its comparative safety *A positive response consists in a sustained increase of arterial pressure* An undue rise of pressure can be abolished by standing erect since the drug also causes orthostatic

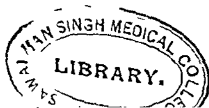
TABLE 5—DIAGNOSTIC TESTS USED IN SUSPECTED PHEOCHROMOCYTOMA (BARTELS AND KINGSLEY)

SUBSTANCE	AUTHORS	DOSE MG	EFFECT ON PRESSURE
Histamine	Roth and Kvale 1945	0 03 (i v)	incr
Mecholyl®	Evans and Guarneri 1946	15 (s c)	incr
Epinephrine	Mayock and Rose 1947	1 (s c)	none
Tetraethylammonium	LaDue Murison and Pack 1947	300 (i v)	incr
Benzodioxane	Goldenberg Snyder Aranow 1947	ca 17 (i v)	decr

hypotension Mecholyl® which normally causes a transient drop in arterial pressure provokes a sustained hyperreactive rise of tension in patients with pheochromocytoma This response is advocated as more reliable than that to histamine The histamine test has had the widest clinical use Its only disadvantages seem to be that certain patients with pheochromocytoma do not show the expected response and that in some patients the reactive rise in pressure is so severe as to cause extreme discomfort severe headache and even collapse In doubtful cases especially in those with a suggestive clinical syndrome two or more of the tests should be used

Treatment consists in excision of the tumor In successful cases it is followed by complete relief from all symptoms Mild diabetes persisted in a patient of Goldner also observed by us In some patients the tumor is bilateral or there are other heterotrophic tumors failure to relieve the condition completely is therefore an

LONGCOPE W T AND WINKENWERDER W L Clinical features of the contracted kidney due to pyelonephritis Bull Johns Hopkins Hosp 53 255 1933
MACKAY A. PROCTOR, L. D AND ROOME N W Hypertension after removal of renal calculus Canad M. A J 50 328 1944
PATTON H S PAGE, E W AND OGDEN E. The results of nephrectomy on experimental renal hypertension Surg Gynec & Obst. 76 493 1943
PLATT R. Severe hypertension in young persons Quart. J Med 17 836 1948
PROUDFIT W L. AND ERNSTENE A. C. Coarctation of the aorta J A M A. 139 985 1949
RAASCHOU F Chronic Pyelonephritis (Copenhagen E. Munksgaard 1948)
RATLIFF R. K. NESBIT R. M. PLUMB R I AND BOHNE W Nephrectomy for hypertension with unilateral renal disease Report of 49 cases J A. M A. 133 296 1947
RODBARD S AND KATZ, L. N The elimination of the effect of the chemical mediator of renal hypertens on Am. J M. Sc. 198 602 1939
ROTH, N The neuropsychiatric aspects of porphyria Psychosom Med 7 291 1945
SCHROEDER H A. AND FISH G W Studies on essential hypertension The effect of nephrectomy upon hypertens on associated with organic renal d sease Am J M Sc. 199 601 1940
SELYE H Textbook of Endocrinology (Montreal Acta endocrinologica Univ de Montreal 1947)
——— The general adaptat on syndrome and the diseases of adaptation J Clin Endocr nol 6 117 1946
SMITH H W Hypertension and urologic disease Am. J Med 4 724 1948
STEELE J M Evidence for general distr but on of peripheral resistance in coarctation of aorta Report of three cases, J Clin. Investigation 20 473 1941
WALDENSTROM J Some observations on acute porphyria and other conditions with a change in the excretion of porphyrins Acta med Scandinav 83 281 1934
WATSON C. J AND LARSON E A Urinary coproporphyrins in health and disease Physiol Rev 2 4 8 1947
WEISS S AND PARKER, F Pyelonephritis Its relation to vascular lesions and to arterial hypertens on Med cine 18 221 1949
WILSON C AND BYROM F B Vicious circle in chron c Bright s disease Experimental evidence from hypertensive rat Quart. J Med. 10 65 1941
ZEMAN F D AND SCHWARTZ, B M The effect of arteriosclerosis on the dynamics of hypertension in the aged J Gerontol vol 3 1948



plete (3) Abdominal with cramping pain vomiting constipation loss of appetite (4) Cardiovascular with hypertension tachycardia

The precise mechanism of the hypertension is not known but since the lesions predominate in nerve tissue and since the hypertension disappears as the attack and nervous manifestations subside there is good reason to assume a causal relationship Whenever the physician encounters a patient with intense psychoneurotic behavior and hypertension he may well test for excess porphyrin by making *the urine very acid or allowing it to stand 24 hours* For more penetrating analysis of the problem the reader is referred to Waldenstrom Watson and Larson or Roth

BIBLIOGRAPHY

ALBRIGHT F Cushing s syndrome Its pathological physiology Harvey Lect (1942 1943) 38 123 1943

ASK UPMARK E On juvenile malignant nephrosclerosis and its relation to disturbances in kidney structure *Acta path et microbiol Scandinav* 6 383 1929

BARTELS E C AND KINGSLEY J W JR Diagnostic tests used in suspected pheochromocytoma Lahey Clin Bull 6 7 1948

BLALOCK A AND PARK E A The surgical treatment of experimental coarctation (atresia) of the aorta Ann Surg 119 445 1944

BRAASCH W F WALTERS W AND HAMMER H J Hypertension and the surgical kidney J A M A 115 1837 1940

BURRAGE W C AND HALSTED J A Adrenal medullary tumor (pheochromocytoma) Case report with successful operation Ann Int Med 28 838 1948

CAHILL G F Pheochromocytomas J A M A 138 180 1948

CHASIS H AND REDISH J Function of the separate kidneys in hypertensive subjects Arch Int Med 70 738 1942

CORCORAN A C AND PAGE I H Methods for the chemical determination of corticosteroids in urine and plasma J Lab & Clin Med 33 1326 1948

CORCORAN A C TAYLOR R D AND PAGE I H Functional patterns in renal disease Ann Int Med 28 560 1948

CRAFOORD C EJRUP B AND GLADNIKOFF H Coarctation of the aorta Thorax 2 121 1947

FRIEDMAN B Experimental hypertension produced by renal ischemia Harvey Lect (1937 1938) 33 237 1938

GOLDNER M G Pheochromocytoma with diabetes *J Clin Endocrinol* 7 716 1947

GOLDRING W AND CHASIS H Hypertension and Hypertensive Disease (New York Commonwealth Fund 1944)

GROSS R E Surgical Treatment for Abnormalities of the Heart and Great Vessels American Lecture Series No 3 Lectures in Surgery (Springfield Ill Charles C Thomas Publisher 1947)

LANGLEY G J AND PLATT R Hypertension and unilateral kidney disease Quart J Med 16 143 1947

than 20/15 mm Hg Hypertensives showed much greater rises the mean being 47 mm systolic and 34 mm diastolic. The response in the same individual was quite constant from day to day in Hines s early experience He is now inclined to admit a wider amplitude of variation and to stress the importance of changes in diastolic pressure in interpretation

Hines has drawn some important theoretical conclusions from his thinking about this test. They justify the closest consideration at the same time complete acceptance must be withheld until further proof is brought. He considers the cold pressor test an index of vascular reactivity Hyperreactivity in his opinion, is an important etiologic factor in essential hypertensión Vascular hyperreactivity may occur as an inherited characteristic of persons who do not have hypertension As such it is believed commonly to represent an antecedent or latent phase of essential hypertension The mass of data he has gathered leaves little doubt that hyperreactivity and hypertension are frequently associated The exact degree and nature of the association remain obscure Until these are elucidated, the use of the test for momentous decisions in an individual normal case is to be discouraged.

The effect of age on the reaction to cold has not been established. Some evidence suggests that the incidence of hyperreaction may increase with age If this becomes established it will be necessary to have different sets of standards according to age levels For this reason it would seem wise to withhold judgment on work in which age groups are compared indiscriminately Doubtless this has led to some of the confusion in the results of various investigators

There is no agreement as to the exact rise in pressure which constitutes pathologic hyperreaction Whether it is + 20/15 or + 30/20 or + 40/30 mm Hg remains to be determined If the limits of the test could be more accurately defined, the prediction value might be greatly improved.

If + 20/15 is accepted as the normal response approximatel

3 Tests Designed to Measure Vascular Responsiveness

BECAUSE OF the wide interest in and use of the cold pressor test, it seems useful to review briefly some of the bases of this test Observations both clinical and experimental, long ago suggested that pressor responses in hypertensive patients were greater than normal For some stimuli this is probably true as we shall see, but for others it is not No evidence is available to show why such selectivity occurs

The various pressor stimuli, such as carbon dioxide inhalation adrenalin,® pitressin,® *exercise, etc, have been investigated but none* has proved more acceptable as a tool for investigation than ice water used in the test of Hines and Brown For this reason this test will be considered at length The examination begins by establishing a control blood pressure level (*important* 20–60 minutes at rest) and is done by immersing a hand up to the wrist in stirred ice water for one minute Blood pressure is measured in the other arm every 30 seconds for the first minute, then every two minutes until the initial level is reached

Hines and Brown divided people with normal blood pressure into two groups (1) normal *hypo*reactors in whom the rise in pressure was less than 20 mm Hg systolic and 15 mm diastolic and (2) normal *hyper*reactors in whom the response was greater

was little difference in the proportion of patients with high initial blood pressure in this series and in a control series of persons who had no urologic or renal disease Further heredity seemed equally important as an initiating factor in the development of hypertension associated with renal disease and in many cases of essential hypertension In short, they do not believe that renal disease is the cause of essential hypertension but rather believe that it occurs with or without urologic renal disease when inherent factors presumably hereditary measurable by the cold pressor test exert their influence

As with surgery of the sympathetic nervous system the use of the cold pressor test antedated a study of its mechanism On the afferent side Wolf and Hardy have shown that it is elicited by a painful sensation due to cold The efferent side has according to Reiser and Ferris two components One is the immediate (one minute response) neurogenic and may consist in splanchnic vasoconstriction the other delayed phase of the pressor response may represent renal pressor stimulation

Agreement has still to be reached on its standardized interpretation To one factor the constancy of the test from day to day we have referred Some investigators find as we do marked diurnal variability A second factor is the relation between the basal level of arterial pressure and the response to cold So far no correlation is established except that in general the lower the control level in relation to casual observations of pressure the greater the response in both normal and hypertensive subjects This paradoxical observation indicates that the standards of normal and hyperreactors may have to depend on their proportion to control pressure Third there seems to be only partial agreement as to the number of hyperreactors in the general population It is important to ascertain this proportion with reasonable certainty because of its bearing on the incidence of hypertension Finally it is somewhat surprising to find that the cold pressor test and some of the other tests notably

85 per cent of persons with normal blood pressure fall into the hyporeactor group The remaining 15 per cent are hyperreactors and may be expected to develop hypertension Whether this is true or not will probably be answered by an extensive experiment now being conducted by Hines Foreshadowing the results is the observation that patients who exhibit an abnormal rise of pressure as the result of the first examination by a physician are much more likely to have hypertension 20 years later than those whose pressures were not increased by this stimulus This appears to be an established fact and was confirmed by a study of the frequency of essential hypertension in Army personnel who at the outset showed only transitory elevations of arterial pressure The frequency with which the hypertension became established as a disease increased with age

The results from the cold pressor test in other investigators hands has been somewhat variable Miller and Bruger found that 39 per cent of normal persons and 76 per cent of essential hypertensives give hyperreactive responses They made the interesting statement that a hyperreactive response in a patient with elevated arterial pressure would exclude the possibility of the hypertension being due to chronic renal disease This confirms the observation of Alam and Smirk that the cold pressor response in chronic nephritis with or without hypertension is not increased Observations by members of our group do not confirm this application of the test but do underline the variability of the response in normotensive and hypertensive subjects and in hypertensives of comparable disease state

A study of Hines and Lander though not strictly comparable has a bearing on these views In 264 patients with various types of urologic disease those who had high normal pressure on their original visit were four to five times as likely to have hypertension subsequently as were those with low normal blood pressure regardless of the type or extent of the urologic or renal lesion There

to lack of care in defining what is meant by a "positive family his tory Indeed, the term is rarely defined in articles dealing with the subject Observations obtained from hospital records are weighted in favor of positive histories in a measure owing to the asking of leading questions those obtained for example during insurance examinations tend toward the negative because of the desire to conceal the unfavorable These circumstances alone if there were not others militate against obtaining a true answer to the problem

There are those who believe the family history is positive in most cases of essential hypertension Thus Hines found a positive family history in 87 per cent of 267 patients with hypertension and in 30 per cent of 608 normotensives The incidence of hypertension was six times greater among a group (1 374 patients) with positive family histories than among those with negative ones Of 300 hypertensive patients averaging 51 years of age 68 per cent had a family history of cardiovascular disease compared with 37 per cent in a control group (O Hare Walker and Vickers) Families in which both parents had normal blood pressure had children in whom the incidence of hypertension was only 3 per cent according to Ayman. But hypertension occurred in 28 per cent of the children with one hypertensive parent and 45 per cent of the children with two hypertensive parents This evidence emphasizes the importance of the hereditary factor

One fact is certainly established namely that there are families who show an unusual predisposition to arterial hypertension For example one family has been observed in which both parents died of cerebral hemorrhage and of their 10 children eight had hyper tension

While there are those who disagree with the observation tha there is a relationship between the response to the cold pressor tes and the family history of cardiovascular renal disease a positiv family history is five times more frequent among normal hyperre actors than among the hyporeactors Further Hines has shown th

that of breath holding do not show the correlation to be expected from similar or identical physiologic mechanisms

To sum up, the consensus is that most essential hypertensives and especially those early in the course are hyperreactors in terms of the cold pressor test Many hypertensives will be recruited from the ranks of the normal hyperreactors that is of those with normal basal pressures and hyperreaction to cold especially when the diastolic pressure rise from cold has been excessive But many normotensive hyperreactors may *not* develop hypertension Hence it is of the greatest importance for the physician to understand that a positive cold pressor test does not infallibly foreshadow the occurrence of hypertension A positive response may be used however, as evidence suggesting the group probability of future hypertension

Hyporeactors, just as those whose arterial pressure is consistently below the usual standards are far less likely to develop hypertension even though put under great strain But likewise, this prognosis is fallible

We believe that this test should be studied further and that it should not be applied as a routine of clinical diagnosis or prognosis without great conservatism in its interpretation The rule of thumb application of present day standards may lead to unjustifiable optimism or pessimism On the other hand the test may ultimately prove clinically useful For this reason its discussion has been extended

Heredity and the Occurrence of Hypertension

Since vascular hyperreactivity is believed by some to be a hereditary characteristic representing an antecedent or latent phase of essential hypertension it is important to inquire into the evidence for the hereditary nature of essential hypertension itself

Much has been written on the subject but few deeply penetrating studies have been made Perhaps much of the diversity of opinion regarding the importance of heredity in hypertension is due



4 Early Stages of Hypertension

As WE HAVE noted the finding of elevated blood pressure is not sufficient ground on which to make the diagnosis of essential hyper tension Some clinicians probably rightly object to the term essen tial hypertension but do not offer a satisfying equivalent nonethe less custom has so established and sanctioned its usage that it does not appear likely to be changed The earlier term hyperpiesia in troduced by Clifford Allbutt has not met with wide acceptance

One of the most elusive and troublesome problems that face the physician is the prognostic differentiation of patients who exhibit *transient* hypertension elicited usually by emotional stimulation into the two groups of those in whom the increase in arterial pres sure is an early manifestation of essential nephritic or arterioscle rotic hypertension and those in whom it has no such significance Especially in these days of health consciousness the number of routine physical examinations done by insurance companies and by employers is constantly increasing and in the process this problem becomes ever more critical without losing much of its obscurity

Nor can the situation be met on either scientific or moral grounds by snap judgments It should not be forgotten that once the diagnosis of essential or nephritic hypertension has been confi dently stated by a qualified reputable physician the patient may be deprived of the benefits of insurance and may even be barred from making his living at the level of his highest skill On a more per

in both twins and family groups the pressor response to cold follows an inherited pattern as a dominant characteristic

Despite the appealing qualities of the view that heredity plays a vital part in the genesis of hypertension evidence to support it has not been compelling A penetrating analysis of the problem is that of Platt Briefly stated his data, which should be extended accord with the view that essential hypertension is a dominant trait A positive family history in a patient with hypertension suggests with a 6 1 probability, that the process is essential whereas a negative family history indicates with only a 3 1 probability that the hypertension is secondary due most often to renal disease Much the same conclusion was reached in a study by Paul Sobye

BIBLIOGRAPHY

ALAM M AND SMIRK F H Blood pressure raising reflexes in health essential hypertension and renal hypertension Clin Sc 3 259 1938

AYMAN D Heredity in arteriolar (essential) hypertension—a clinical study of the blood pressure of 1 524 members of 277 families Arch Int Med 53 792 1934

FELDT R H AND WENSTRAND D E W The cold pressor test in subjects with normal blood pressure Report of observations on 350 subjects with special reference to the family history Am Heart J 23 766 1942

——— The family history in arterial hypertension A study of 1 376 insurance examinations Am J M Sc 205 61 1943

HINES E A JR Ranges of normal blood pressure and subsequent development of hypertension J A M A 115 271 1940

——— AND LANDER H H Factors contributing to the development of hypertension in patients suffering from renal disease J A M A 116 1050 1941

MILLER J H AND BRUGER M The cold pressor reaction in normal subjects and in patients with primary (essential) and secondary (renal) hypertension Am Heart J 18 329 1939

O HARE J P WALKER W G AND VICKERS I C Heredity and hypertension J A M A 83 27 1924

PLATT R Heredity in hypertension Quart J Med 16 111 1947

REISER M F AND FERRIS E B JR The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension J Clin Investigation 27 156 1948

ROBINSON S C Hypotension The ideal normal blood pressure New England J Med 223 407 1940

RUSSEK H I Blood pressure in the aged A study of 1 000 elderly male subjects Am Heart J 26 398 1943

SOBYE P Heredity in Essential Hypertension and Nephrosclerosis (Copenhagen E Munksgaard 1948)

WOLF S AND HARDY J D Studies on pain Observations on pain due to local cooling and on factors involved in the cold pressor effect J Clin Investigation 20 521 1941

4 Early Stages of Hypertension

As WE HAVE noted, the finding of elevated blood pressure is not sufficient ground on which to make the diagnosis of essential hypertension Some clinicians probably rightly object to the term essential hypertension but do not offer a satisfying equivalent nonetheless custom has so established and sanctioned its usage that it does not appear likely to be changed. The earlier term hyperpiesia introduced by Clifford Allbutt, has not met with wide acceptance

One of the most elusive and troublesome problems that face the physician is the prognostic differentiation of patients who exhibit transient hypertension elicited usually by emotional stimulation into the two groups of those in whom the increase in arterial pressure is an early manifestation of essential nephritic or arteriosclerotic hypertension and those in whom it has no such significance Especially in these days of health consciousness the number of routine physical examinations done by insurance companies and by employers is constantly increasing and, in the process this problem becomes ever more critical without losing much of its obscurity

Nor can the situation be met on either scientific or moral grounds by snap judgments It should not be forgotten that once the diagnosis of essential or nephritic hypertension has been confidently stated by a qualified reputable physician the patient may be deprived of the benefits of insurance and may even be barred from making his living at the level of his highest skill On a more per

sonal level, the probability of making the patient unhappy is great

Despite the fact that contemporary knowledge does not allow the differentiation to be *made with assurance physicians must set* it as a goal which investigation should achieve The approach to this problem may be facilitated by a tentative classification so that as methods become available the results can be applied logically to differential diagnosis The following nomenclature may prove useful

Significance of Transient Elevations of Arterial Pressure

1 *Simple vasomotor lability* Transient and irregular episodes of elevated blood pressure chiefly systolic, associated with increased heart rate and usually some obvious emotional stimulus The characteristic clinical and laboratory picture of essential hypertension is not present and does not necessarily develop

2 *Prehypertension* These patients respond as do those with simple vasomotor lability and will probably develop hypertension

3 *Neurogenic hypertension* These patients have early established hypertension but on a neurogenic basis i e with signs and symptoms of nervous hyperactivity

4 *Early essential hypertension* These patients have established hypertension possibly on a humoral basis with early arteriolar disease

This is only a tentative classification, subject to alteration or dis card as more facts become available But it has value in emphasizing the nature of the problem of early hypertension We may now consider these groupings in more detail

Vasomotor Lability as Opposed to Prehypertension

Arterial pressure fluctuates with changes in the internal and external environment several of which have been reviewed (p 19) In most but not in all persons these fluctuations are not great A minority show violent changes well into the abnormal range under what seem to be moderate or even unobserved stimuli Are these

persons then suffering from very early essential hypertension or will they surely acquire it?

It is not uncommon to see people with moderate elevation in blood pressure during one or even several examinations in whom the pressure is normal 10 years later Probably too much has been made of these exceptions for unfortunately, the pressure is more commonly found at higher levels on subsequent examination The problem is how to differentiate those with simple vasomotor lability from those who are prehypertensive At present there is no sure way But it is salutary to realize that there is a difference

Transient hypertension is more common with advancing age and is then more often the precursor of persistent hypertension This experience confirms our own and restates the principles of Hines and Brown But the quandary remains since even at age 50 only half of those with transient increases of arterial pressure develop persistent disease while a significant number (roughly 10 per cent) who have not shown this sign also become hypertensive

At least two approaches immediately present themselves for the solution of the problem (1) There may be a qualitative difference in the mechanism of the transient elevations in blood pressure In the group with simple vasomotor lability the blood pressure response is sharp but not pathologic in the group with prehypertension the response is a manifestation of early morbid underlying change (2) The underlying pressor response in both groups may be the same but the response in the hypertensive is quantitatively prolonged hence the one group develops essential hypertension the other does not. These views might quite evidently be subjected to experimental analysis and there is urgent need that this be done

There are certain observations which if established as applying to the patient under examination suggest the occurrence of simple vasomotor lability as opposed to prehypertension Unfortunately they are only suggestive

A high incidence of hypertension in the family suggests the

diagnosis of prehypertension The psychologic make up should be of great value, but unfortunately agreement on what constitutes a pattern leading to hypertension is insufficient for close definition If the rise in arterial pressure occurs in the absence of obvious *stimuli* some weight is added to the side of prehypertension The response to the cold *pressor test may be and often is, more intense* in the prehypertensive especially the rise in diastolic pressure but the differences may be insufficient to aid in differential diagnosis If in doubt it seems wise to postpone diagnosis until the patient has been studied for a sufficiently long period to establish a definite trend In the present state of knowledge and technic too hasty diagnosis surely does more mischief than delay over a period no *matter if it is several years long during which the diagnosis can be* more firmly established

During a period of such indecision it is better to calm the fears of the patient by erring on the side of optimism than to risk the danger of engendering a neurosis by a too lugubrious attitude As his confidence is gained a review of his life status may point to remediable factors in social and domestic life the correction of which may solve the issue *temporarily at least The importance of the* decision which must be made or *postponed is* adequate basis for a painstaking examination If even then no decision can be reached it may be useful to conceal one s fears and to ask the patient to return for an annual physical examination

It is important at this stage to exclude other causes of hypertension such as pyelonephritis and urogenital abnormalities Indeed *this is one of the useful functions subserved by a careful investiga*tion of patients who exhibit unusual rises in arterial pressure

Although all of these factors are of value in disclosing prehypertensives still they are not sure enough The addition of a few more definitive examinations would significantly increase the certainty of diagnosis This is one of the important and persistent problems of cardiovascular disease

NEUROGENIC HYPERTENSION

Symptoms and signs of a disordered nervous system in certain hypertensives long ago led to the belief that in some at least, the disease was caused by increased vasomotor activity But objective evidence was not obtained that this was so Indeed so extravagant and uncritical were some authors in their espousal of this view that a reaction against it was initiated which culminated in the belief that the nervous system had nothing whatever to do with hypertension. Current opinion again favors its importance in the genesis of certain cases of hypertension

It is well to remember that the term neurogenic signifies that the hypertension has its origin in the nervous system probably as a result of increase in the number of impulses carried by the vasomotor nerves Such a concept may be premature for strict proof that hypertension is ever so caused in human beings is not at hand But certain scanty evidence suggests that it might be

It is possible that the neurogenic element reaches its zenith in the early phase of hypertension to be reinforced or supplanted later by the humoral mechanism

An interesting example of the possibility of a neurogenic origin of hypertension is that found in one of identical twins It is generally assumed that the hereditary pattern of identical twins is alike and hence the presence of a disease in one and not in the other tends to minimize the importance of the hereditary component Renal blood flow and glomerular filtration rates were similar in the hypertensive and the normotensive twin but the psychologic patterns differed widely These facts suggest that the psychologic pattern is of primary etiologic significance

From bedside observation two clinical pictures have been observed which strongly suggest the importance of the participation of the nervous system in certain types of hypertension The first of these hypertension with manifestations of a neurosis is probably

diagnosis of prehypertension The psychologic make up should be of great value, but unfortunately agreement on what constitutes a pattern leading to hypertension is insufficient for close definition If the rise in arterial pressure occurs in the absence of obvious stimuli some weight is added to the side of prehypertension The response to the cold pressor test may be, and often is more intense in the prehypertensive especially the rise in diastolic pressure but the differences may be insufficient to aid in differential diagnosis If in doubt it seems wise to postpone diagnosis until the patient has been studied for a sufficiently long period to establish a definite trend In the present state of knowledge and technic too hasty diagnosis surely does more mischief than delay over a period no matter if it is several years long during which the diagnosis can be more firmly established

During a period of such indecision it is better to calm the fears of the patient by erring on the side of optimism than to risk the danger of engendering a neurosis by a too lugubrious attitude As his confidence is gained a review of his life status may point to remediable factors in social and domestic life the correction of which may solve the issue temporarily at least The importance of the decision which must be made or postponed is adequate basis for a painstaking examination If even then no decision can be reached it may be useful to conceal one s fears and to ask the patient to return for an annual physical examination

It is important at this stage to exclude other causes of hypertension such as pyelonephritis and urogenital abnormalities Indeed this is one of the useful functions subserved by a careful investigation of patients who exhibit unusual rises in arterial pressure

Although all of these factors are of value in disclosing prehypertensives still they are not sure enough The addition of a few more definitive examinations would significantly increase the certainty of diagnosis This is one of the important and persistent problems of cardiovascular disease

condition from hyperthyroidism that the serum cholesterol is normal or elevated rather than low. His observations indicate that a barbituric acid derivative known in this country as mebaral® given in a dose of 200 mg two or three times daily, causes a remission of most of the signs of the diencephalic syndrome apparently through its action as a hypothalamic sedative. Schroeder and Goldman have added to the diagnosis of the diencephalic syndrome a test in which intradermal injection of 0.25 mg of histamine base precipitates a typical attack in a few minutes.

The syndrome was called diencephalic because almost identical signs can be brought on by diffuse stimulation of the diencephalon in human beings. It is worth recognizing it not only so that ill advised medication or operation may be avoided but because the prognosis seems to be on the whole much better than for the more usual varieties of essential hypertension.

BIBLIOGRAPHY

AYMAN D The early diagnosis and early treatment of arteriolar (essential) hypertension New England J Med. 205 474 1931

VAN BUCHEM, F S P The hypertensive diencephalic syndrome Acta med. Scandinav 130 575 1948

FRIEDMAN M., AND KASANIN J S Hypertension in only one of identical twins Report of a case with consideration of psychosomatic factors Arch. Int. Med 72 767 1943

LEVY R. L. HILLMAN C. C. STROUD W D AND WHITE P D Transient hypertension Its significance in terms of later development of sustained hypertension and cardiovascular renal diseases J A M. A. 126 829 1944

MASTER A. M Cardiovascular problems in war Hypertension and the Navy Bull. New York Acad Med 19 704 1943

PAGE, I H A syndrome simulating diencephalic stimulation occurring in patients with essential hypertension Am. J M. Sc. 190 9 1935

ROGERS W F AND PALMER, R. S Transient nervous hypertension as a military risk New England J Med 230 39 1944

SCHROEDER H A AND GOLDMAN M A Test for the presence of hypertensive diencephalic syndrome using histamine Am. J Med. 6 162 1949

THOMPSON C E., AND WITHAM A. C Paroxysmal hypertension in spinal cord injuries New England J Med 239 291 1948

the more common but also the less well defined A few psychiatrists have attempted to find a characteristic psychiatric pattern which might have an etiologic connection with the hypertension but their results have not carried complete conviction (see p 92) and can hardly apply to all patients who suffer from this disease There seem to be common denominators in the mental pattern of many hypertensives (p 94) This is a new vista and requires intensive investigation in a combined study by internists and psychiatrists The second the hypertensive diencephalic syndrome presents a clearly defined clinical picture apart from psychic phenomena, but the evidence in favor of its being of neurogenic origin is based only on analogy Regardless of its mechanism it is important that it be differentiated clinically because of its different course and prognosis

The Hypertensive Diencephalic Syndrome

This syndrome was first described as most frequent in young and *middle aged women though it is occasionally seen in men It is* characterized by hypertension of the labile sort more especially by periodic appearance of a blotchy blush which extends down over the face and upper chest seldom if ever involving the limbs Indeed the extremities may be cold pale or have a dusky mottled hue during an attack Over the area of blush are minute beads of perspiration Tearing or merely watering of the eyes may occur without an associated emotional counterpart or with only a minor change in effect Tachycardia and hyperperistalsis are common These episodes occur without apparent cause or may be brought on by embarrassment and excitement Graves disease is often diagnosed because of these signs and because the thyroid gland usually exhibits slight diffuse enlargement and the basal metabolic rate is often elevated from about + 10 to + 30 Subtotal thyroidectomy and antithyroid drugs do not benefit these patients but the superficial similarities too often lead to their use

Van Buchem noted as a point in differential diagnosis of this

dox that some clinicians caution against regarding it as a highly serious disease or as a disease at all while still they acknowledge it as the greatest single cause of death

Indeed the physician is often so frustrated by it all that he openly wishes that the sphygmomanometer had never been invented and that we were back in the days of the hard and soft pulses And he so continues until five minutes or five days later he finds that it really is a very useful tool in a tight place and then if he is American thanks the shades of Crile and Cushing the surgeons who told him about it

A prime fact in dealing with hypertension is that it begins and may persist for years without causing any symptoms Diastolic hypertension is probably most often accidentally found whether in a routine physical or during an examination for insurance employ ment or for armed service In its early phases the disease is asymptomatic This absence of symptoms shows that the vascular tree can for variable periods adjust and accommodate itself to the impact of arterial hypertension A corollary is that *presence of symptoms* early in the disease indicates in a few patients a rapid failure of *this* adjustment but in most suggests a concomitant neurosis In early hypertension then symptoms if *present* are usually those of an anxiety state and such signs as occur result from increased vasomotor irritability and take the form of cold extremities pallor dizziness vague tensions and vaguer pains Signs and symptoms due to hypertension appear only as the results of arterial and arteriolar damage make themselves felt

Familial morbidity is significant in the anamnesis In our experience 30–40 per cent of patients have close relatives who have had hypertension It may have expressed itself as heart disease kidney disease or strokes but close *questioning* will leave little doubt as to the *nature* of the underlying hypertensive process The age these relatives have reached gives some notion of the probable resilience of the patient s own vascular system Inheritance of a poor

SECTION II

5 Essential and Malignant Hypertension

Essential Hypertension

Essential hypertension makes itself known by such a variety of signs and symptoms that it is hardly possible to present a typical clinical picture Nevertheless certain changes considered as a group delineate it with a fair degree of clarity The exhaustive examination includes measurements which add greatly to definition such as those of renal blood flow and secretory capacity

On the basis of contemporary evidence essential hypertension can be defined as a morbid state in which fluctuating systolic and diastolic arterial hypertension occurs in association with characteristic arteriolar vasoconstriction

Many people have the impression that essential hypertension is almost exclusively a disease of middle or old age when it commonly assumes its florid form It is increasingly clear that the process usually begins much earlier than the fourth or fifth decade probably in the early twenties but its onset goes unrecognized It is to this early group that we have already given attention

So insidious is the onset of this disease and so asymptomatic may be its course for long periods that its true and evil nature is not soon or sufficiently recognized Perhaps this accounts for the para

like jumping out of my skin." Some note that they must constantly be moving unable to relax unable to avoid controversy They feel caught in endless rounds of unsatisfying activity Again this is not a characteristic pattern of hypertension though it seems more common in hypertensives than in other people Hypertensives are thought of as high strung emotional aggressive persons But there are many exceptions. Often the patient is so well integrated that it takes some time to find not only the cause of the tension which is successfully concealed beneath a thick protective coating but even that tension exists'

Still there is a residue of patients whom life seems to have treated kindly they seem to face it without resentments euphorically feeling with Pangloss that this is the best of all possible worlds No other neurotic manifestations are discernible but hypertension is present just the same

Thus the onset of hypertension is usually insidious and the patient is usually unable to determine the time of its inception Either it is discovered by accident, or the onset of vascular failure is announced by the eyes heart or kidneys The disease is well advanced by this time

As los of cardiac adaptation begins dyspnea appears on exertion. The patient may be uncomfortable when sleeping flat in bed or unable to eat a full meal without shortness of breath Vague sensations of oppression in the chest are not unusual Precordial pain occurs, ranging from mild, almost unnoticed discomfort to the severe pangs of angina pectoris Fortunately the latter type is not common Ed ma of the ankles also indicates beginning cardiac insufficiency Often the patient notices that the heart is heaving and turbulent, but in many hypertensives it is quiet and the rate not increased. Tachycardia is more common in early hypertensives with psychoneurotic b ckgrounds and usually these are the patients who complain of palpitation

vascular elastica and the need for one which can withstand hypertension often coincide and together jeopardize the patient's life Systolic hypertension in elderly relatives, usually merely the hemodynamic result of senile fibrosis (arteriosclerotic hypertension p 39), does not imply the early demise of a younger relative who has essential hypertension Manifestly also, a relative who has reached the age of 70 and has withstood essential hypertension must have an arterial tree that is more than ordinarily good

Headache (see p 242) is probably the most common symptom Often it occurs in the morning wanes with the breakfast coffee and finally disappears before midmorning or noon There seems to be no characteristic location, but frequently it is in the occipital region Severity varies from a feeling of stiffness and tightness in the neck to an excruciating throbbing pain

Some believe that most headaches among hypertensives are associated more with an underlying psychoneurosis than with the hypertension Somewhat supporting this view is the observation that the height of the blood pressure and the severity of headaches do not parallel each other There is often a history of migraine

Some patients complain of a feeling of constriction in the scalp especially over the vertex It is a sensation seldom experienced by patients with normal blood pressure

Perhaps the next most common complaint is that of easy fatigability Especially toward midafternoon the patient feels completely done in even after an uneventful morning Other hypertensives show fatigue only after prolonged strain and appear able to carry on long after normal persons are tired Though fatigue is common it is by no means a symptom characteristic of hypertension

Some patients are able to date the onset of hypertension with reasonable accuracy by changes they note in emotional tension From easygoing persons they may become irregularly irritable intolerant and inconsiderate The complaint is often expressed I feel

THE MALIGNANT SYNDROME OR MALIGNANT HYPERTENSION

Physician have long recognized that the clinical course of arterial hypertension is exceptionally variable The lives of some patients are only moderately shortened others succumb within periods measurable in months In 1914 Volhard and Fahr emphasized these differences by the clinical terms benign and malignant in their concept of nephrosclerosis and pointed out that the benign form of hypertension may at any time turn malignant They and others believed that patients with rapidly fatal course had faulty kidneys hence the terms malignant nephrosclerosis and genuine contracted kidney Insufficient regard was paid the blood vessels in the rest of the body until Fishberg and others pointed out the error Even now the fact that the emphasis is probably not adequately distributed is reflected by continued use of the term nephrosclerosis (p 286)

In 1928 Keith Wagener and Kernohan presented a classic description of 81 patients with arterial hypertension characteristic retinopathy adequate renal function and rapidly fatal outcome They designated this the syndrome of malignant hypertension Subsequently their observations were amply confirmed

The mechanism of the malignant syndrome is not clear In dogs Goldblatt and Keyes have been able to produce a clinical picture resembling that in human beings by constricting the renal arteries severely The picture is characterized by hypertension terminal renal insufficiency and petechiae and large hemorrhages in many internal organs especially the alimentary tract There is dissecting hemorrhage through or rupture of the walls of severely hyalinized or necrotic arterioles or rupture of capillaries A characteristic retinopathy is also noted Elevation of blood pressure and renal insufficiency with hypoxia were considered two of the necessary conditions for development of the necrotic arterioles and hemorrhages

With Taylor, we have become impressed by the fact that nocturia may precede dyspnea and edema as a sign of imminent congestive failure This nocturia, like that of famine edema is due to storage of water during the day and its discharge by night It is distinguished from nocturia of renal origin by the concentration test (p 271) which demonstrates a normal or only slightly impaired maximal urinary specific gravity

Disturbance of the kidneys in a form recognizable by the patient does not occur early Later hyposthenuric nocturia may appear Despite the fact that the kidneys may causally participate in the disease, *they give little indication of culpability* (pp 247 ff)

We have spoken of some of the manifestations indicating involvement of the nervous system especially headache and irritability But there are others and more serious Vertigo tinnitus insomnia fatigue weakness and other less well defined complaints seem to have their origin in the disordered activity of the nervous system One of the most dramatic and frightening episodes in the life of a hypertensive may be the appearance of hypertensive encephalopathy (p 236) Usually thrombosis and hemorrhage occur only late in the disease Clinical evidence strongly suggests that small thrombi form in various portions of the brain long before damage to any large area appears and these focal areas of softening may account for some of the odd assortment of signs and symptoms such as tingling in the fingers and hands paresthesias and numbness Transitory and usually incomplete palsies probably are to be explained on this basis *These are not lightly to be dismissed They in association* with nuchal headaches may be prodromes of apoplexy

Disturbances of vision are rare until quite late in the course of the disease If they occur the physician should immediately suspect the presence of the malignant syndrome for here retinal deterioration proceeds at a rapid pace Occasionally during essential hypertension thrombosis of one retinal artery occurs which may cause disturbed vision in the area nourished by the vessel

ened and their lumens reduced, especially by medial hypertrophy Hyalinization and necrosis usually occur only as end stages Changes are found even in vessels in skeletal muscle Hyperplastic sclerosis with thickening of the media and narrowing of the lumen is observed.

The necrotizing arteriolar lesions may represent an acceleration of the same process observed in already accelerated senescence which constitutes the arteriolar sclerosis of essential hypertension Or has some qualitative change occurred quite independent of the fundamental factors causing essential hypertension?

Do these patients have a disease quite distinct from essential hypertension? The answer is probably that they do not rather that it is a syndrome that may complicate the course of a number of diseases characterized by hypertension Thus certain of its clinical manifestations may be observed in patients with pyelonephritis glomerulonephritis pheochromocytoma, polyarteritis and so on

Most patients exhibiting the malignant syndrome have had a prolonged period of essential hypertension In these it comes as a rapid deterioration which strikes the patient down with dramatic suddenness But there is also a documented group of cases in which no significant period of hypertension foreshadows the events to come In these signs of the malignant syndrome are present from the first, and the course occasionally is run in weeks or months

Thus malignant hypertension is seen as an intensification of the vascular disease of hypertension the cause of which is not known.

Clinical picture—The malignant syndrome usually occurs in early or middle life seldom in old age It is believed to be more common in men than in women and this has been our experience

Opinion differs as to the frequency with which hypertension has occurred in the families of these patients Our patients in whom the syndrome appeared without a preliminary episode of essential hypertension have not shown an abnormal incidence of familial cardiovascular disease A higher incidence is to be expected in those who

It is not yet firmly established that renal insufficiency is necessary for the initiation of this syndrome in dogs hence it may well bear a closer resemblance to the one in human beings than might appear on the surface Early in the course, renal excretory function may be normal, though this seldom lasts long But the fact that it is sometimes normal raises doubts as to the participation of renal excretory functions in the genesis of the syndrome

Byrom and Wilson made interesting experiments in rats which suggest the importance of arterial pressure If the renal artery of one kidney is constricted and hypertension results arteriolar necrosis may develop in its formerly normal partner They believe that these vascular and parenchymal lesions duplicate those in human beings, but pathologists have not been wholly convinced Selye s experiments on *the endocrine kidney similarly demonstrate the importance* of high arterial tension in the genesis of arterial and arteriolar disease Byrom and Dodson produced acute arterial necrosis in rats by sudden severe increases of arterial tension alone

Fishberg has stressed the importance of elevation of the diastolic pressure as a genetic factor in the malignant syndrome It is usually greater than 130 mm Hg However, occasional patients with the fully developed syndrome have diastolic pressure consistently well below this figure *While* sustained elevation of *diastolic pressure is* doubtless important in causing its development it does not seem to be the only factor

Clearly the cause or the mechanism of this dangerous phase of hypertension is not surely known

The changes observed at autopsy have been the subject of much study Of particular interest to us are the vascular changes These vary somewhat in different organs but in general they consist of severe arteriolosclerosis and in addition necrosis *with fibrinoid degeneration* especially of the renal arterioles and endarteritis (cellular intimal thickening) of small renal arteries Arteriolar necrosis may be limited to the kidneys The cerebral arterioles become thick

precordium occurs frequently Nocturia and edema of the ankles appear An electrocardiogram usually shows flattening or inversion of the T waves in leads I and II along with the usual left axis deviation and evidences of myocardial strain

Kidney function as measured by urea clearance or ability to concentrate urine is usually normal or slightly reduced early in the course or is at first unchanged from that *measured* during the phase of essential hypertension But good function will not long be maintained precipitate falls being the rule Bursts of gross hematuria are common and protein excretion increases 0 5–5 Gm per 24 hours

This stage may be punctuated by episodes in which *transient* (i e from 10 minutes to a day or two) paralysis or aphasia appears Often bizarre albeit usually insignificant psychologic changes occur These are attributed to minute thrombi in the vessels of the brain which cause areas of focal necrosis

As the terminal phase approaches cardiac failure becomes intensified. Cardiac enlargement often occurs at a remarkable rate and may be attributed more to dilatation than to hypertrophy As a result, protodiastolic gallop sounds are frequent. Renal failure also seems to accelerate oliguria or anuria may alternate with polyuria Renal clearance and blood flow fall to low levels and waste products are retained in the blood Sight may be severely reduced or lost. Nausea vomiting and loss of appetite occur followed by alarming loss of weight Convulsions may be anticipated in many patients

Anemia develops rapidly and the plasma proteins may be terminally reduced Blood urea nitrogen is high and urea clearance greatly depressed Increasingly severe proteinuria macroscopic hematuria and cylindruria are usually *present*

The patient becomes drowsy and may die in uremia Others die of cardiac failure and a few of cerebral hemorrhage So rapid may be the deterioration that sometimes no decision can be made as to which one of these delivers the fatal blow

experience a hypertensive prelude We have the impression that most patients with primary malignant hypertension show little or none of the psychologic pattern common in essential hypertension

It has not been possible to predict the onset of the malignant syndrome in patients with established hypertension Severe head ache, some shortness of breath fatigue weakness loss of weight nocturia, edema of the ankles and above all blurred vision appear early and should call the physician s attention to the possibility of its onset

Funduscopic examination at this stage usually shows early papilledema fresh hemorrhages arteriolar constriction and exudate likely to be more marked in the left than in the right eye Most observers do not believe the malignant syndrome should be diag nosed in the absence of papilledema this has been our experience as well Exceptions occur Still, the clinical diagnosis of malignant hypertension in the absence of papilledema is difficult and treacher ous

It is usually thought that the papilledema is due to increased intracranial pressure Indeed Fishberg has observed that cerebro spinal fluid pressure usually increases before papilledema appears Measurement has shown that in general papilledema and increased pressure although often associated do not parallel one another Papilledema occurs without increased intracranial pressure in some patients and cerebrospinal fluid pressure is sometimes increased without the appearance of papilledema hence the increased pressure probably is not the sole cause

Examination of the heart may show moderate enlargement but nothing pathognomonic of the syndrome Tachycardia is common since it tends to maintain cardiac output without the need for hyper trophy left axis deviation may not develop As the morbid state progresses signs of cardiac strain appear A gallop rhythm may come and go Dyspnea is complained of and pain referred to the

presumably as the result of arteriolar constriction and afferent arteriolar sclerosis In some patients the afferent arteriolar sclerosis and constriction are so severe that despite the greatly increased arterial pressure and constriction of the glomerular efferent arteri oles intraglomerular hydrostatic pressure seems not to be increased above the normal or is even low Such patients like the glomer ulonephritics develop hypoproteinemia.

The history given by the patient is of prime importance in mak ing the differentiation The story of Bright s disease is usually quite typical especially when the patient has been studied during its course

Thus the correct diagnosis can usually be made from the an amnesis and thorough examination of the heart and kidneys

So Called Menopausal Hypertension

The age period of onset of the menopause is also the one in which essential hypertension is most likely to occur Little wonder then that clinicians have imputed a specific causative role to the menopause and that the term menopausal hypertension has be come common coin in medical linguistics

To ascertain whether the menopause does in fact cause or pre dispose to hypertension 200 women of different ages were studied, most of whom had undergone hysterectomy and ovariectomy Hy pertension was no more common in those surgically castrated than in normal women of the same age Menopausal symptoms could be related to lifelong vasomotor and emotional instability Thus loss of ovarian secretions does not of itself cause or predispose to essen tial hypertension The hypertension of the menopause is only es sential hypertension probably accentuated by the emotional turmoil of the period. There is no menopausal hypertension

Treatment with the effective estrogens such as stilbestrol at times supplemented with thyroid aids in restoring emotional equi librium in such patients and hence often reduces arterial pressure

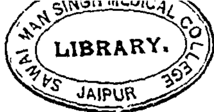
Differentiation of Malignant Syndrome with Renal Failure and Terminal Glomerulonephritis

It is of some practical as well as theoretical importance to find means of differentiating the malignant hypertensive syndrome with renal failure, as it appears with or without the substrate of essential hypertension and terminal glomerulonephritis The practical reason for making the differentiation is that patients with terminal glomerulonephritis tend to live much longer than those with the malignant hypertensive syndrome

Terminal glomerulonephritis is characterized by very low rates of glomerular filtration (urea clearance less than 10 per cent of normal) and tubular secretory capacity and usually a higher rate of proteinuria often exceeding 5 Gm per day Despite the low level of renal excretory function such patients survive four times as long as do those with the malignant syndrome in renal failure The changes in renal function are in accord with the structural changes found in the kidneys The lesions are glomerular and capillary associated with great parenchymal destruction and fibrous replacement

Clinical signs of heart failure tend to occur much less frequently and later in terminal Bright's disease Cardiac enlargement is also slower in appearing and the cardiac shadow is more often of the globular variety suggesting dilatation in contrast with the left ventricular enlargement of the malignant syndrome Left axis deviation and T wave and S–T segment changes occur three times more commonly in the malignant syndrome than in terminal glomerulonephritis Thus malignant hypertension is characterized by the presence of significant myocardial damage It is probably because this damage is not as severe in nephritis that nephritic patients tolerate a much greater degree of renal excretory loss

In the malignant syndrome with renal failure intraglomerular hydrostatic pressure is usually elevated and the flow of blood through the residue of intact tubular tissue is diminished the latter



6 Physical Examination

PATIENTS WITH early essential hypertension show little that is ab normal on physical examination except a variable increase of arterial pressure The most significant findings may be those which indicate that the elevated blood pressure is due to some disease more easily remediable than essential hypertension or at least one whose nature is more clearly understood For this reason the examiner must bear in mind some of the wide variety of causes of hypertension Though some are uncommon and many are rare the search for them should be unremitting

The lack of physical signs and symptoms in early hypertension can prevent many patients from seeking medical advice or once having received it from abiding by it. We have pointed out that the first evidences of illness in many patients seem to be psychologic disturbances During physical examination one is often struck by the bodily expressions of tension The brow is knit reactions are hyperactive and instability of the vasomotor nerves is evidenced by sweating blushing palpitations and cold extremities The physical tension has its parallel in the mental sphere usually this is all too apparent

But are there any physical changes in the early stages by which the diagnosis can be made? Except for slight constriction of the ar terioles in the eyegrounds and at times increased force of the heart beat there are none *The diagnosis of very early hypertension by*

BIBLIOGRAPHY

BYROM F B AND DODSON L H The causation of acute arterial necrosis in hypertensive disease J Path & Bact 60 357 1948

CORCORAN A C AND PAGE I H *Differential diagnosis of terminal glomerulonephritis and malignant hypertension* I Renal aspects Ann Int Med 21 747 1944

DEROW H A AND ALTSCHULE M D The nature of malignant hypertension Ann Int Med 14 1768 1941

ELLIS A Malignant hypertension (Schorstein lecture) Lancet 1 977 1938

FISHBERG A M Hypertension and Nephritis (4th ed Philadelphia Lea & Febiger 1939)

GOLDBLATT H Studies on experimental hypertension VII Production of the malignant phase of hypertension J Exper Med 67 809 1938

MURPHY F D AND GRILL J So-called malignant hypertension A clinical and morphologic study Arch Int Med 46 75 1930

PAGE I H A clinical study of malignant hypertension Ann Int Med 12 978 1939

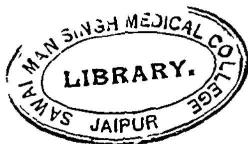
PICKERING G W *The relationship of benign and malignant hypertension* J Mt Sinai Hosp 5 916 1942

TAYLOR R D KOHLSTAEDT K G RICHTER A B AND PAGE I H Differential diagnosis of terminal glomerulonephritis and malignant hypertension II Cardiac aspects Ann Int Med 21 765 November 1944

——— CORCORAN A C AND PAGE I H Menopausal hypertension A critical study Am J M Sc 213 475 1947

——— AND PAGE I H *Signs and symptoms of impending cerebral hemorrhage* J A M A 127 384 1945

WAGENER H P AND KEITH N M Diffuse arteriolar disease with hypertension and the associated retinal lesions Medicine 18 317 1939





6 Physical Examination

PATIENTS WITH early essential hypertension show little that is abnormal on physical examination except a variable increase of arterial pressure The most significant findings may be those which indicate that the elevated blood pressure is due to some disease more easily remediable than essential hypertension or at least one whose nature is more clearly understood For this reason the examiner must bear in mind some of the wide variety of causes of hypertension Though some are uncommon and many are rare the search for them should be unremitting

The lack of physical signs and symptoms in early hypertension can prevent many patients from seeking medical advice or once having received it from abiding by it We have pointed out that the first evidences of illness in many patients seem to be psychologic disturbances During physical examination one is often struck by the bodily expressions of tension The brow is knit reactions are hyperactive and instability of the vasomotor nerves is evidenced by sweating blushing palpitations and cold extremities The physical tension has its parallel in the mental sphere usually this is all too apparent

But are there any physical changes in the early stages by which the diagnosis can be made? Except for slight constriction of the arterioles in the eyegrounds and at times increased force of the heart beat, there are none *The diagnosis of very early hypertension by*

physical examination rests on the finding of fluctuating elevated diastolic arterial pressure which persists when all the possible variables of the measurement are excluded and when a truly searching study reveals no other cause for the condition

The rate at which the heart, arteries and arterioles lose their ability to adapt to the presence of hypertension varies widely Once the process is well established, the degree and rate of vascular deterioration may be estimated from changes in two arteriolar beds—those of the eyegrounds, which are seen directly, and those of the kidney, indirectly visualized by tests of renal function and from the changes in cardiac function The phase of beginning loss of vascular adaptation is graded 2 in the schema of Keith and Wagener (p 27) since it is marked by beginning retinal arteriolosclerosis and some increase of vasoconstriction This phase may persist almost unchanged for years Occasionally it is short lived passing rapidly into a more severe state

With deterioration come evidences of structural injury, particularly in the heart, brain and kidneys the beginnings and course of which and the means of eliciting their presence we discuss elsewhere The disease may progress slowly to cardiac renal and cerebral circulatory failure may assume the aspect of malignant hypertension or in rare cases may regress to a pattern like that of early hypertension leaving a residue of sclerotic arterioles

Ophthalmoscopic examination remains by far the most useful method for detecting the rate of advance and the severity of vascular deterioration Most extrarenal vascular areas have little significance because no clinical methods are available by which to estimate the state of the vessels until they have become seriously diseased Particularly to be regretted is the lack of precise clinical means of determining the condition of the cerebral vessels Procedures for examination of the renal and cardiac vascular areas are given in the appropriate chapters

EYEGROUND EXAMINATION

No part of the physical examination equals that of the eye grounds in assessing the stage and later, determining the progress of the disease Indeed once hypertension has been diagnosed the ophthalmoscope becomes more useful than the sphygmomanometer

The eyeground examination is worth a much more detailed discussion than can be given here Practice rather than reading leads to facility in this examination and in the interpretation of its results No convenient opportunity to make and repeat the examination should be neglected Adequate dilation of the pupils with paredrine hydrobromide® (1 per cent solution) euphthalmine® (5 per cent) or homatropine (1 per cent) is necessary for thorough study and no other type of study is worth while Eserine (0 1 per cent) may be instilled after the examination to speed the return of pupillary con striction and accommodation. Excess light should be excluded from the room. Both patient and physician should be comfortably placed. Observations of the fundus should be made in a systematic compass pattern so that every portion is examined

Hypertensive disease is reflected in the eyegrounds primarily in the arterioles and secondarily in the retina The vascular changes may be functional and therefore reversible or structural and largely irreversible The functional changes consist in varying degrees of arteriolar constriction The structural lesions are usually lumped to gether as sclerosis or arteriosclerosis These terms are imprecise First the affected vessels are arterioles rather than arteries Second the term sclerosis may signify any one or any combination of three distinct lesions

The most common of these lesions in the hypertensive is hyalin ization of the arteriolar wall—the same productive and degenerative change that hypertension imposes on arterioles elsewhere as they lose their capacity to resist its onslaught (p 110) The two other

forms of vascular change interpreted as sclerosis are, respectively, senile decrescent fibrosis and atheromatosis They appear and develop quite independently of intimal hyalinization which alone is the characteristic change in this disease It would probably be better to displace the ambiguous term sclerosis by some such term as arteriolar hyalinization or even arteriolosis which would carry most of the meaning of this specific abnormality

The walls of normal retinal vessels both arteriolar and venous, are probably invisible It is the column of blood they contain which can be seen Obviously narrowing of the blood column is the principal indication of the presence of vasoconstriction But narrowing of the column can occur independently of vasoconstriction when the vessels atrophy in the course of nonpathologic senile or atrophic regression, when the lumen is reduced by intimal hyalinization in hypertensive disease or when the central retinal artery is occluded Since narrowing is not of itself an indication of vasoconstriction vessels which are very differently affected may superficially look very much alike The observer must be at some pains to record and extend his observations before forming a definitive impression

But an interpretive impression must be forthcoming if the examination is to be useful and the interpretation is most helpful if it both defines the character and evaluates the degree of change This estimate may be made as by Keith and Wagener in a graded summary of abnormalities commonly concurrent in hypertension (p 27) or as we would prefer by a separate evaluation of each element of abnormality

Grading of Retinopathy

Constriction of Arterioles

Grade 1 Narrowing as indicated by slight reduction of the blood column ratio in corresponding arterioles and veins below the normal of arteriole 8 and vein 10

Grade 2 Increased reduction of ratio to arteriole 6 vein 10 The

angle of branching is more acute the arterioles seem straightene There may be segmental vasospasm.

Grade 3 Ratio reduced to arteriole 4 vein 10 The arterioles n longer extend into the periphery of the retina.

Grade 4 Extreme narrowing of arterioles arterioles less than 4 vein 10 The vessels seem to disappear after they leave the disk. Usual associated with displacement of the vein at the point of crossing

Arteriolar Hyalinization

Grade 1 Increase in the width and brightness of the light strea due to decreased translucency Beginning arteriovenous displacemer

Grade 2 Exaggeration of grade 1 the walls of the smaller arteriol assume a glassy quality and the arterioles in the absence of severe va constriction, may be more than normally tortuous. Definite arteri venous displacement.

Grade 3 The vessel walls appear separate from the blood colun The small arterioles become opaque and the larger yellowish. Arter venous compression so great that the vein is engorged beyond the po of crossing. Increased arteriolar tortuosity Beginning perivascular whi ness in the retina close to larger arterioles.

Grade 4 The walls of the arterioles are silvery white The pe vascular reaction extends to smaller branches. The blood column greatly reduced in caliber and is irregular There is intense arteriovene compression.

Hemorrhages and Exudates (grade each separately)

The sum of the changes present in the two eyes is used in gradi

Grade 1 One to three areas.

Grade 2 Three to six

Grade 3 Six to 10

Grade 4 More than 10

Papilledema

See pp 86 f

Since the observer's experience is the ultimate criterion in examination there is an unavoidable subjective factor Howe by grading from 1 to 4 plus in each category of distinguisha change using always the same criteria of interpretation the obser should not find the evaluation difficult

forms of vascular change interpreted as sclerosis are respectively, senile decrescent fibrosis and atheromatosis They appear and develop quite independently of intimal hyalinization which alone is the characteristic change in this disease It would probably be better to displace the ambiguous term sclerosis by some such term as *arteriolar hyalinization* or even *arteriolosis*, which would carry most of the meaning of this specific abnormality

The walls of normal retinal vessels both arteriolar and venous are probably invisible It is the column of blood they contain which can be seen Obviously, narrowing of the blood column is the principal *indication of the presence of vasoconstriction But narrowing* of the column can occur independently of vasoconstriction when the vessels atrophy in the course of nonpathologic senile or atrophic regression, when the lumen is reduced by intimal hyalinization in hypertensive disease or when the central retinal artery is occluded Since narrowing is not of itself an indication of vasoconstriction vessels which are very differently affected may superficially look very much alike The observer must be at some pains to record and extend his observations before forming a definitive impression

*But an interpretive impression must be forthcoming if the ex*amination is to be useful and the interpretation is most helpful if it both defines the character and evaluates the degree of change This estimate may be made as by Keith and Wagener in a graded summary of *abnormalities commonly concurrent in hypertension* (p 27) or as we would prefer by a separate evaluation of each element of abnormality

Grading of Retinopathy

Constriction of Arterioles

Grade 1 Narrowing as indicated by slight reduction of the blood column ratio in corresponding arterioles and veins below the normal of arteriole 8 and vein 10

Grade 2 Increased reduction of ratio to arteriole 6 vein 10 The

ossing for a common adventitia here surrounds both vessels (Friedenwald) Arteriovenous nicking is at first due to the vein s having been displaced from its course Such displacement is com mon when the arteriole is thickened by hyaline But it also occurs when the vein is pulled from its course by arteriolar retraction whether due to intense vasoconstriction or to atrophic regression nicking although a common indication of intimal hyalinization is not a specific sign.

Most observers agree that retinal arteriolar hyalinization like arteriolar hyalinization elsewhere follows rather than precedes the onset of hypertension although some patients show it early and others go on for years without much evidence of it Repeated exam inations demonstrate the rate of change The record of this rate prog nostically is comparable to a record of the changes in heart size

This type of change characteristic of established and advancing hypertension is to be sharply distinguished from atheromatosis and from senile regression Atheromatosis (p 110) may occur at any age although more common in elderly patients It is largely inde pendent of hypertension and often associated with diabetes mellitus Its chief interest here lies in the possibility that central retinal atheromas may block the vessel suggesting severe retinal arteriolar constriction while atheromas in the arterioles may be taken as evi dence for local areas of hyalinization Senile decrescent fibrosis (p 108) which affects all the vascular tree in the very aged is mentioned for the same reason

The fundal changes resulting from advanced hypertension are hemorrhages exudates and edema

Hemorrhage usually appears early in the course of retinopathy and persists throughout although in a few patients exudates and papilledema predominate The hemorrhages of hypertensives usu ally can be distinguished from those due to local arteriolar or venous diseases such as occur in diabetes mellitus and those which form in hemorrhagic diatheses such as leukemia The hemorrhage in hyper tension spreads from close to the arteriole between the fibers of the

The aim is to record separately the respective degrees of arteriolar constriction and intimal hyalinization (so-called sclerosis), of papilledema, retinal hemorrhage and exudates The major difficulty as we have seen, lies in the distinction of the type and degree of arteriolar change

The normal fundal arterioles are smaller in caliber than the accompanying veins and there is no compression of the vein by the arteriole at the point of crossing The normal arteriolar branching is wide the curves of the vessel s course are broad and the out line of the column of blood may be followed well out into the periphery of the fundus Fundal arteriolar vasoconstriction is to be expected in established hypertension When it appears it may involve all the vessel wall or may be segmental, changing in locus from hour to hour Segmental vasospasm, although not infrequent in essential hypertension is more characteristic of the acute hypertension of glomerulonephritis or toxemia of pregnancy Generalized vasoconstriction shortens the arterioles They become straightened their angle of branching becomes more acute and they can no longer be traced out into the fundal periphery They thus give the impression of having been pulled in as by retraction of the retinal artery into the optic nerve

Retinal arteriolar constriction in hypertension is probably more *of humoral than of nervous origin But the activity of the vasomotor* nerves is shown in the increased caliber of the vessels which has been repeatedly observed after successful lumbodorsal sympathectomy This is probably a reflex vasodilation since the area involved is far from that which was denervated

As vascular adaptation to stress begins to fail the intima of the retinal arterioles is replaced and thickened by hyaline The vessel wall then becomes in a degree visible that is it ceases to be translucent and becomes a reflecting surface As the process advances the arterioles become irregularly tortuous and ultimately the vessel walls can be seen There is no adventitia to separate the media of the arteriole from the subendothelium of the vein at the point of

crossing for a common adventitia here surrounds both vessels (Friedenwald) Arteriovenous nicking is at first due to the vein s having been displaced from its course Such displacement is common when the arteriole is thickened by hyaline But it also occurs when the vein is pulled from its course by arteriolar retraction whether due to intense vasoconstriction or to atrophic regression Nicking although a common indication of intimal hyalinization is not a specific sign

Most observers agree that retinal arteriolar hyalinization like arteriolar hyalinization elsewhere follows rather than precedes the onset of hypertension although some patients show it early and others go on for years without much evidence of it. Repeated examinations demonstrate the rate of change The record of this rate prognostically is comparable to a record of the changes in heart size

This type of change characteristic of established and advancing hypertension is to be sharply distinguished from atheromatosis and from senile regression. Atheromatosis (p 110) may occur at any age although more common in elderly patients It is largely independent of hypertension and often associated with diabetes mellitus Its chief interest here lies in the possibility that central retinal atheromas may block the vessel suggesting severe retinal arteriolar constriction while atheromas in the arterioles may be taken as evidence for local areas of hyalinization Senile decrescent fibrosis (p 108) which affects all the vascular tree in the very aged is mentioned for the same reason

The fundal changes resulting from advanced hypertension are hemorrhages exudates and edema

Hemorrhage usually appears early in the course of retinopathy and persists throughout, although in a few patients exudates and papilledema predominate The hemorrhages of hypertensives usually can be distinguished from those due to local arteriolar or venous diseases such as occur in diabetes mellitus and those which form in hemorrhagic diatheses such as leukemia The hemorrhage in hypertension spreads from close to the arteriole between the fibers of the

nerve fiber layer of the retina These fibers run parallel to the surface of the fundus The hemorrhages are therefore flame shaped and lie close to and parallel to the arterioles In contrast, the spots of bleeding in disorders of the blood or in diabetes are punctate or petechial and often round and appear in the deeper layers of the retina often from the efferent veins of the deep capillary plexus Occasionally hemorrhage occurs from local arteriolar or venous occlusion More commonly it is the result of retinal venous thrombosis It is accompanied by retinal edema and exudates in the affected quadrant but is independent of hypertension

The reason exudates form as hard white spots or as cotton wool is not clear Some think them the result of local edema which after reabsorption of the fluid leaves a lipid residue Others suggest that the lipid is deposited by aggregated macrophages which enter the edematous area Still others believe that spastic or structural arteriolar occlusion produces foci of retinal necrosis giving rise to grayish spots Exudates like hemorrhages are graded by the sum of their number in the two eyes

The grading of papilledema is not always easy The edges of the normal nerve head are sharply defined the lateral more clearly than the nasal The physiologic cup is usually readily seen The color of the disk varies widely even in health Extreme pallor suggests the presence of optic atrophy Marked redness may signify the congestive hyperemia which precedes papilledema The first stage of papilledema (1 plus) consists in hyperemia loss of physiologic cupping and obliteration of the lateral disk margin The second stage (2 plus) is an extension of this phase with definite elevation of the nerve head by 1–2 D in the third stage (3 plus) the retina is also edematous and elevation of the disk has advanced to 3 or 4 D In the fourth stage (4 plus) the edges of the nerve head cannot be distinguished from the retina and there are more than 4 D of swelling

Edema of the retina is usually a late sign in hypertension Early it is observed as a grayish haziness especially around the papilla

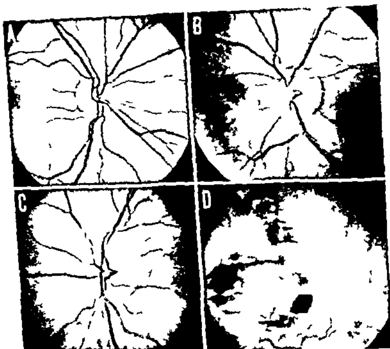


Fig. 1.—Eyeground changes. *A*, normal eyeground. *B*, early essential hypertension exhibiting grade 1 constriction and sclerosis. *C*, more advanced essential hypertension showing grade 2 sclerosis and constriction. The A-V crossing phenomenon is shown. *D*, malignant hypertension showing severe hemorrhage and exudate formation in macular region. (See also illustrations on pages 329 and 348.)

Localized areas of effusion may lead to detachment The latter is particularly common in toxemias of pregnancy, when all the cranial tissues are severely edematous

Fully developed retinopathy was formerly termed albuminuric retinitis because of its frequent association with renal disease However, the diversity of its origin (toxemia of pregnancy, malignant hypertension terminal glomerulonephritis) shows that this inclusive term has outlived its usefulness

The significance of the qualitative and quantitative changes in the eyegrounds lies in the fact that here alone is a vascular area with the principal victims of hypertension the arterioles exposed to view Early in the course of the disease constriction is the only finding Later with loss of adaptation arteriolar hyalinization gains and progresses The onset of the malignant syndrome is usually heralded by the appearance of papilledema, sooner or later followed by hemorrhages and exudates

The appearance of small, discrete scanty retinal hemorrhages in the absence of papilledema or of other characteristics of the malignant syndrome is one of the elements establishing the prognosis of cerebral hemorrhage

The illustrations from fundus photographs (Fig 1) demonstrate several aspects of the retinal pattern in hypertensive disease

BIBLIOGRAPHY

BALLANTYNE A J Retinal changes associated with diabetes and with hypertension Comparison and contrast Arch Ophth 33 97 1945

FISHBERG A M AND OPPENHEIMER B S The differentiation and significance of certain ophthalmoscopic pictures in hypertensive disease Arch Int Med 46 901 1930

FRIEDENWALD J in Ridley F and Sorsby A (eds) Modern Trends in Ophthalmology (New York Paul C. Hoeber Inc 1940)

KOCH F L P Retina in systemic vascular hypertension A clinical study of the caliber of the retinal arterioles and the retinal arterial diastolic blood pressure Arch. Ophth 26 565 1941

TAYLOR R D AND PAGE I H Signs and symptoms of impending cerebral hemorrhage J A M A 127 384 1945

WAGENER H P Retinal vascular changes in hypertension Ann Int Med 4 222 1930

——— AND KEITH N M Diffuse arteriolar disease with hypertension and the associated retinal lesions Medicine 18 317 1939

7 Psychotherapy and Related Problems

MEDICINE OF THE nineteenth century applied in practice the Cartesian theory of separation of mind and body Alexander quoted Zweig who wrote Disease meant now no longer what happens to the whole man but what happens to his organs the natural and original mission of the physician the approach to disease as a whole changed into the smaller task of localizing the ailment and identifying it and ascribing it to an already specified group of diseases This type of medical thinking has influenced many present-day teachers and practitioners of medicine It underlies much of the uncritical reverence still given quantitative measurements it impels the physician to examine and treat urine not the diabetic and blood pressure not the hypertensive But the reacknowledgment of the unity of man and of the change in the whole man implicit in disease is well under way Alan Gregg among others hails this trend in many fields as a foreshadowing of things to come

Essential hypertension as much as or more than any other disease bears closely on this problem. In any well established case it is a disease of full serried organic expression in many cases it seems to be psychogenic in every case it has its repercussions in the life and thinking of the patient. To the degree that they can be considered apart mental disturbances can be related to hypertension as cause result or complication

Psychogenesis

Mental disturbance might give rise to such a disease as hypertension (1) by acting as primary efficient cause or (2) by acting as a trigger a co-ordinate cause which converts pre existing organic potentiality into actual disease In the first instance, the mental upset must be taken as sufficient explanation for the presence of the disease either by statistical examination of groups or by demonstration of a specific mental pattern in individual human beings suffering from hypertension

The effect of emotional upsets on arterial pressure has in the few years it has been recognized passed into the familiarity of lay slang Readers of Sunday supplements are earnest if inaccurate students of *sphygmomanometric lie detectors and in the tragicomic* funnies observe the antics of the terrible tempered Mr Bang and speculate about his blood pressure If lay knowledge is sometimes exasperating it is not because we wish it to be less but rather because it is composed of muddied trickles from a Pierian spring Thus when he speaks of hypertension the layman applies the simile of boiler and steam engine—mind and body Mechanically the analogy is inexact for it supposes that outspoken rage and exteriorized anxiety are necessary pathways to high blood pressure chronologically it is behind the times this is the electric age A better analogy is that of a dynamo whose current is directed exteriorly into motors of conscious action and interiorly into condensers of nervous muscular vascular and glandular tissue which buffer and smooth the exterior discharge When exterior force puts a brake on the motors or when the dynamo runs so quickly that they cannot use the current the condensers become overloaded The concentration of tension is then reflected in a disorder of some sort this may take the form of disordered visceral or vascular function In this analogy the mental origin of such a disease as hypertension might be repressed over active or unsatisfactorily directed emotional tension Granting the

possibility of psychogenesis in hypertension the question is whether or not the strain itself is specific so that it is an adequate explanation of the disease or whether its expression depends on a predisposition of one condenser the vascular tree

An example of the statistical approach is Donnison s measurements of arterial pressure in 1 000 male natives of the Kenya reserved lands He divided the subjects into groups of about 100 in each decade from 15 to 80 or more years estimated age The levels of pressure were the same as those of Europeans and Americans until about age 40 At this age the standards for white races show an increase in pressure level possibly owing to inclusion of mild cases of hypertension In contrast, both systolic and diastolic pressures progressed somewhat downward in the Kenya group Transient elevations of pressure were not uncommon among the natives in only two cases (0 2 per cent) was there question of persistent elevation of pressure Further Donnison found no cases of raised arterial pressure in 1 800 admissions to a native hospital

The contrast between these observations among the Kenya people and those in white groups is striking and it is increased when the comparison is made with American Negroes for among them hypertension is common begins early in life and is often severe The conditions of their life are different from those of Kenya Colony The American Negro s life pattern is seldom of his own choosing the lower levels of the culture of the people with or for whom he works seek sometimes to defend themselves by excluding him or find in him someone to be better than He may feel that statutes are ambiguous unequally applied, and the basic law of the land contradicted in practice The Kenya Negro lives on a land and in a culture undisputedly his own and his aspirations and possibilities in life are defined and accepted almost from the moment of his birth The greater frequency of hypertension in the Jewish race might also be adduced To these examples we may add the small decrease of average arterial pressure in Europeans who live in tropical lands

where most of the mental work is done by the subject races Thus from the aspect of hypertension, it seems more blessed to give in dignity than to sustain it These examples might be accepted as experiments in the mass psychogenesis of hypertension were they not clouded by differences of diet racial admixture and mode of life

That emotional stress may worsen the status of an established hypertensive or play a part in converting prehypertension into early hypertension and that release from strain may improve the patient s condition are well known The critical physician recognizes the de crease in blood pressure which occurs during the patient s first visits or when he meticulously assumes a touted regime even one as un impressive as a ritual of the pink pill He is also familiar with the rise of pressure associated with personal sexual domestic or social tension Physicians who do not recognize this relation unconsciously encourage their patients to drift away into the care of colleagues and quacks whose powerful asset is only the confidence they create and their intuitive knowledge of human nature Such observations, how ever thoroughly documented merely establish mental disturbance as an accomplice to the fact they do not indicate that it can be a primary cause To establish it as a primary cause it must be shown (1) that hypertension can arise *de novo* from mental causes non specific or specific or (2) that the disease as such can be abolished by appropriate psychotherapy

The methods available for the definition of a hypertensive per sonality are those of psychology which operate at conscious levels those of psychoanalysis which attempt to delineate the unconscious and the imprecisions of empiric practice Since the first two claim precision, the examiner must also use more than ordinary care in the selection of his group excluding those in whom the disease seems wholly somatogenic and secondary rather than essential those whose realization of invalidism had distractingly overlain the pat tern of onset with the stresses of personal fright and familial concern should also be rejected He should also have means of showing

whether or not a similar pattern occurs in people who do not have real or potential hypertension

The psychologic method as applied by Hamilton to a group of young males some of them showing mild hypertension—although none was told the purpose of the study—weakens the layman s mis conception of the hypertensive personality which identifies hyper tension and hyperkinesis Rather subjects with hypertension were found to walk and move more slowly to be less dominant and self assertive more introspective than the normotensives of similar age and environment. Many of the hypertensives were prone to blushing and to outbursts of anger the latter contrasting with their custom arily subdued mien

The analytic method is necessarily limited to small groups so that reports are made on the basis of seven cases or only one These patients must have been thoroughly convinced of emotional dis order or they would not have made themselves available for such a study so that the selection of cases is heavily weighted in favor of psychic dominance In brief the psychoanalytic method indicates that the lives of hypertensive patients are vectors of two opposed trends The one is a wish for submissive passive childlike depend ence, the other is an ambitious aggressive desire for achievement Psychic trauma prevents the mature expression of either wish and the clash of the two in repression causes psychic tension parallel tendencies of psychic and arterial tension can be demonstrated These mingled opposite desires explain much of the difficulty of those who try to define the hypertensive personality in two-dimen sional terms such as those a cartoonist would convey with the stroke of a pen Unfortunately for etiologic definition a similar imbalance of desires underlies many other *psychosomatic* and psychologic syndromes

A pattern of trend rather than causality might be drawn by the physician who has seen through 20 years the transformation of eager expressive competitive tendencies into genteel niceness which

subsided into inhibition lame expression and bursts of flaming resentment falling back in shamed composure into a desire only to keep the peace He may be able to trace the change from expression to inhibition to some precipitating reverse which threw the patient back onto his shallow emotional and intellectual resources The wife may say He was never like this before, it was then he took up drinking for some of these patients find a release in alcohol and by its aid expand to soberly unattainable resistance to criticism and ease of expression in which they may seek to establish their dominance by promiscuous sexual activity But from alcohol they gain hangovers from promiscuity venereal disease, and from both remorse As inhibitory tendencies gain control they may lose the ability to make decisions and therefore the capacity for responsible work While the mind retreats the mouth becomes more active so that they may smoke and drink to excess and eat themselves into corpulence They may terminate as did many in Dunbar's series in dependence on the public funds

Rennie from another approach sums up the hypertensive personality as one of life long emotional lability and anxiety and in addition to the usual traits mentioned we would include perfectionism ambition and over attention to bodily symptoms The outstanding emotional pattern appears to be one of resentment He noted that this pattern is delineable in patients in whom emotional factors seem to be apparent from the outset of the disease

A somewhat more precise definition of the nature of the patients basic mental quirks was obtained by Binger and his colleagues in their study of the personality of hypertensives They found a rather uniform pattern of failure psychic and somatic but did not pretend causally to relate one to the other An excellent study (Gressel *et al*) the more fascinating and convincing because it was controlled established on what seem adequate grounds that hypertensives show generally significantly higher degrees of association with anxiety obsessive compulsive behavior and subnormal asser

tiveness than do groups with definite psychoneurosis or definite chronic disease of organic origin This work confirms and validates a widespread clinical impression

Still we do not know the mechanism by which conscious anxiety often unassociated with other neurotic traits but accompanied by suppressed, sometimes volcanically erupting rage can co-operate with other factors in causing the onset of the disease Acute rage leads to elevation of blood pressure by the neurohumoral channels of sympathetic release But chronic and concealed rage is not as obvious a cause nor is the organic pattern of the disease consistent with hyperadrenalinemia Failure to remember the difference is ground for many limping analogies

Thus in rage or anxiety there are usually pallor and tachycardia and while renal ischemia may develop the evidence is entirely in favor of a wholly sympatheticoneurogenic explanation of such physical changes Among them only increased arterial tension and in some degree renal ischemia characterize essential hypertension Points of transition may still be found One such is the adrenocortical discharge elicited by epinephrine Another is the curious relation of nervous function to renal pressor activity What seem to be instances of such transitions are the usually temporary hypertensive states seen in troops after battle or in civilians who have experienced such major disasters as that at Texas City in 1948

Since similar if not identical mixtures of trends are associated with other psychosomatic diseases or in the absence of somatic disturbance it may be that the hypertensive personality can cause the disease only in association with some hereditary pattern of organic vascular-endocrine susceptibility The two may mingle in varying degree in provoking hypertension The importance of psychic factors is shown in the fact that symptoms (headache dizziness vague pains insomnia weakness) may have been full blown during the stage of adaptation when circulation was quantitatively normal

One aspect of the transition from personality disorder with

subsided into inhibition lame expression and bursts of flaming resentment falling back in shamed composure into a desire only to keep the peace He may be able to trace the change from expression to inhibition to some precipitating reverse which threw the patient back onto his shallow emotional and intellectual resources The wife may say He was never like this before it was then he took up drinking for some of these patients find a release in alcohol and by its aid expand to soberly unattainable resistance to criticism and ease of expression in which they may seek to establish their dominance by promiscuous sexual activity But from alcohol they gain hangovers from promiscuity venereal disease and from both remorse *As inhibitory tendencies gain control they may lose the* ability to make decisions and therefore the capacity for responsible work While the mind retreats the mouth becomes more active so that they may smoke and drink to excess and eat themselves into corpulence They may terminate as did many in Dunbar s series in dependence on the public funds

Rennie from another approach sums up the hypertensive personality as one of life long emotional lability and anxiety and in addition to the usual traits mentioned we would include perfectionism ambition and over attention to bodily symptoms The outstanding *emotional pattern appears to be one of resentment* He noted that this pattern is delineable in patients in whom emotional factors seem to be apparent from the outset of the disease

A somewhat more precise definition of the nature of the patients basic mental quirks was obtained by Binger and his colleagues in their study of the personality of hypertensives They found a rather uniform pattern of failure psychic and somatic but did not pretend causally to relate one to the other An excellent study (Gressel *et al*) the more fascinating and convincing because it was controlled established on what seem adequate grounds that hypertensives show *generally significantly* higher degrees of association with anxiety obsessive compulsive behavior and subnormal asser

and progress The latter is the more obvious and practical aspect. Treatment here consists in the recognition removal or acceptance of the hazards and difficulties of everyday life including the added one of hypertension In essence it consists in the application to hypertension of the recognized technics of physical and mental hygiene To deal with the psyche as cause is more difficult and as we have seen much less certain ground for therapy The basic problem is one of anxiety with opposed aggressive and passive tendencies which often render treatment difficult for the physician who is unwilling to recognize the possible gain to the patient from free expressions of aggressiveness and to put up with the snubs criticism quarreling and broken appointments The whole aim at first is to place the patient at ease and to assume confidently and naturally the direction and review of nearly every phase of his life In certain cases when the psychic imbalance seems paramount and insuperable by ordinary means recourse should be had to a psychiatrist preferably one with some interest in the problem But a cure is not to be expected from any form of psychotherapy though some may have considerable palliative effect.

Related Problems

Related problems in therapy arise initially from consciousness of illness and later from the presence of real or the threat of future disabilities The levels of mental activity at which these appear are that of conscious anxiety—the need for acceptance of hypertension and what limitations it may impose—and that of the unconscious where the sense of illness increases a sense of dependency on the physician which may be already hypertrophied From a mixture of the two levels there develops a host of queries spoken or not about the details and orientation of life their effect on the course of the disease and the opportunities of using them for good In meeting this problem the physician seeks to establish the mood and consciousness of equanimity the rule he would prescribe is that of the

(assumed) constitutional susceptibility to frank vascular disease is discussed under the heading neurogenic hypertension (p 65) This term is proposed to include patients whose hypertension is mild, who do not show vascular degeneration or renal pressor activity and whose symptoms, sometimes disabling are not traceable to organic dysfunction Some of these patients progress to established essential hypertension with advancing vascular disease and symptoms consistent with renal pressor hyperactivity Although the transition has been observed in only a few cases, pairs of fathers and sons have been studied in whom the father shows full blown essential hypertension and the son of similar build and outward personality, only the neurogenic phase

Thus, the accumulation of evidence, statistical, psychologic, analytic and empiric suggests that a process primarily mental may presumably in co operation with unknown neurohumoral factors result in essential hypertension and that this mingling mechanism acts in an uncertain but large proportion of those who suffer from the disease But the evidence (p 92) lacks (1) the characterization and (2), as we shall see the proof of cure which would establish psychogenesis Once the disease is established continuance of the mental distress can only speed the onset of physical disability while, in the interval, it accounts for much of the misery the patient feels The physician s problem is onerous He must try to recognize the personality patterns which may lead to hypertension and by modifying and protecting them attempt its prevention In established cases he must guard against the temptation to deal only with the solid entrancing, satisfying details of physical measurement Rather, when psychologic factors seem significant he must give of time and ungrudging emotional energy as a firm directing guide

PROCEDURE

Psychotherapy in hypertension is concerned with the psyche either as a cause of the disease or as an intensifier of its symptoms

the error of understatement. In this way they become personally able to co-operate in the management In so doing they are aided in their acceptance of their condition

The regime —We have already discussed the unconscious trends commonly found in the hypertensive patient Where they have been etiologically significant neither the discovery of his disease nor the onset of disability with loss of vascular adaptation removes them but as we have suggested either condition may increase the aspect of dependency The physician s duty is to accept the proffered de pendency and gradually transfer it back to the patient as confidence in himself and understanding of his condition are increased This carries a heavy responsibility for the temptation to impose a rigid life program often physiologically unsound on a patient who seems to be floundering for the lack of one is more than a physician who is domineering or busy or merely lazy can easily resist

Thus there will be a demand for a rule of life which will cover the questions of work and leisure rest and play the moraloids alcohol and tobacco use of tea and coffee the magic of diet and often the problem of insomnia One of us has covered most of these elsewhere the text, intended for the patient s use was necessarily general The degree to which its recommendations should be indi vidually modified rests with the physician At least at the outset when the patient hangs on his every word and indecision the phy sician s do s and don t s should be stated definitely probably more dogmatically than scientific accuracy might justify and since the problem is one of keeping the patient well rather than making him an invalid the number of rules should be limited and their charac ter well proportioned to the patient s emotions and intellectual and financial possibilities

Work and play Rest and leisure —These problems are upper most in the minds of all who have to earn a living or keep a house Ruthless insistence on rest is to be avoided. Rather as Karl Mennin ger pointed out *In arterial hypertension for example where there*

good the moderate life, carefully adjusted to the patient's inner and outer needs his aim is primarily the avoidance of unnecessary invalidism and if possible amelioration of his patient's physical condition To a varying degree the modes of treatment may be directed to both psychic and somatic panels of the disease Hence their discussion here

The patient's initial problem of conscious acceptance and painless integration of his condition into the fabric of his life depends partly on his intellectual approach The philosophic approach of patients whose aggressiveness has been the more obvious facet of their mental working molded as it commonly is to their inchoate desires, may have been close to that of the jungle The jungle ethic is not comforting to one who is sick or preparing to be sick Rather the patient thrown back on himself and the physician may have to be helped in his problem of accepting the achievement of a more kindly point of view

It is not in the physician's province to organize the patient's ethical approach nor would imposed and incomplete acceptance do more than increase tension Rather since the rational acceptance of unknown presumably incurable illness is more than even the most stoic souls can bear without a larger outward vision of the world, the physician should not block the available avenues of expression—physiologic religious philanthropic To the degree that he can understand the selected expression the physician may be able to aid and encourage his patient

Understanding the disease—The extent to which the physician should explain the disease the form it individually takes and the complications which may follow is a matter of nice judgment Some patients are terrified by any approach to the truth and are entirely willing to place themselves wholly in the hands of the physician An explanation however hopeful may do more harm than good Those with a larger degree of emotional independence are often greatly aided by an account of their condition which avoids

Diet—The problem of diet is considered in Chapter 16

The minor vices—Alcohol The questions of the use of alcohol and tobacco by the hypertensive patient are surrounded by idols and fears which afflict the physician as often as the patient With alcohol the question is not that of alcoholism or dipsomania Ordinary use of alcohol by the social drinker is complicated by his specific fears and the possibility of excess with resultant fatigue excess smoking and hangover Alcohol is to be avoided when fears are great or excess is inevitable

The beneficial effects of moderate ingestion of alcohol which some have claimed seem to lie in a feeling of well being and release from tension This rather than its vasodilator effect is the basis for the occasional prescription of a glass of sherry before dinner or a hot toddy before retiring More effective vasodilators especially of the coronary vessels and other hypnotics are available when alcohol is not acceptable There is some evidence that cholesterol atherosclerosis of rabbits can be prevented by the concurrent administration of alcohol some pathologists believe that atherosclerosis is uncommon in chronic alcoholics Neither observation seems devoid of emotional bias nor is it likely that socially acceptable and physically tolerable quantities of alcohol have any effect of this sort. In any case a recent study indicates that the alcoholic s freedom from arteriosclerosis is due merely to the fact that he dies young

Tobacco The question of the use and abuse of tobacco is complicated by the fact that certain patients especially in the morning seem intolerant to inhalation of nicotine This is reflected in sympathetic stimulation weakness fatigue and vasoconstriction particularly significant when it affects the coronary circulation Among such patients the use of tobacco is to be interdicted or strictly limited. But the indication is specific to the individual and is not a systemic treatment of hypertension

It is not easy to decide on the advantages of denicotinized cigars and cigarets They may relieve the tension which arises from

is a vascular response to the anxiety associated with emotional conflict, the former proscription of exercise and work seems to have been a step in precisely the wrong direction I am confident that the death of some hypertensive patients has been hastened by physicians who removed them from the only available form of aggression to which they had access

Useful successful work is a normal, desirable condition of life and with most people necessary The value of work to the hypertensive lies in work as a part of the moderate life The adjustment is made by limitation, sometimes by extension, of its conditions to a level of satisfactory achievement consistent with physical well being Work is not an end in itself, but a means The patient should be brought rapidly to this realization Work, when interrupted by rest is demonstrably more productive for the hypertensive, as it is for the normal individual The evening rise of blood pressure may be interrupted by repeated periods of rest The patient will more easily achieve the mingling of work and rest by following a regular schedule, for instance a half hour before lunch an hour before dinner and bed at ten o clock

The form of these periods of rest is less important than the degree of relaxation they induce Some rest in quiet and silence, others read and others listen to the radio In each case recumbency and absence of interruption should be assured

The problem of the leisure hours and the possibility of play is met by definition of their purpose which is that of surcease and solace Play should fulfil the criterion of pleasure since the hypertensive patient may not excel without more than a desirable degree of physical effort and mental strain competitive play or play in the line of business should be discouraged Play does not mean personal athletic participation It may lie in a hobby in a hike in the companionship of children or in participation in community or social effort. The usefulness and type of play selected depend on the degree of pleasure realized and the concomitant release from tension

Insofar as there has developed a vicious cycle in which the fear of not sleeping prevents sleep the assurance that rest may be obtained by relaxation without sleep is useful Empiric rules such as those outlined by one of us for the patient s use may prove beneficial Most of these are matters of ordinary common sense Certain patients may be led to a purposeful satisfying and soluble train of thought by application of Jacobson s method of progressive relaxation

When insomnia is a real problem it is wisely met by the use of hypnotic drugs Their recommendation may be prefaced by the explanation that they are not dope for the fear of them is widespread owing partly to misinformation and partly to neurotic resistance The choice is made from the character of the insomnia Difficulty in getting to sleep is countered by a quick acting barbiturate The same drug given on retiring in enteric coating may aid those who wake at cockcrow Alternatively a long acting barbiturate such as phenobarbital or amytal[8] (¾–1½ gr) may be given an hour before retiring Should tension persist during the day the dose may be repeated once or twice

Certain patients will find chloral hydrate more useful than the barbiturates It is given in 5 10 or 15 gr dosage either in simple solution or in a mixture such as hypertensive *mixture* It has a

℞	Syr ac hydriotici	0 48
	Potasii bromidi	16 0
	Chloral hydratis	32 0
	Muc. acacia	60 0
	Syr aurantii	120 0
	Aq dest. q s ad	240 0

S g 4 cc once twice or three times a day

rapid action and it may be that its taste *ordinarily* objectionable is sometimes a virtue

The menopause is commonly associated with insomnia At least half the women who find this period one of great tension formerly showed neurotic trends which the menopause only exaggerates The underlying neurosis will not be cured by *estrogen* The tension may

the restriction of smoking to the extent that the nicotine is actually removed and because their expense and unaccustomed flavor keep the smoker within bounds of nicotine intake Where there is question of a specific intolerance to smoking partial denicotinization does not seem to us to solve the problem

There is no reason to doubt the validity of Pearl's statistical demonstration that nonsmokers live longer than those who smoke The degree of causal association between smoking and longevity is *widely open to question There may be none Women who usually* smoke less than men in any case live longer, smoking itself is a *symptomatic means of oral gratification and of release from psychic* tension It is generally agreed that psychic tension shortens the length of life Thus to the extent that smoking relieves tension it might be argued that in certain cases it lengthens the useful span of the patient's existence

Thus in the face of the indecisions and contraindications which surround both alcohol and tobacco the physician who would interdict or recommend them is on tenuous ground These problems should be approached on the basis of specific and objective evidence avoiding alike an exaggeration of the evils or of the possible benefits of either substance

Coffee and tea The use of these substances like that of alcohol and tobacco is a matter of individualization Tolerance to the *caffeine they* and some cola drinks contain is widely variable Tachycardia sweating tremor and light headedness indicate excess The jumpy patient may not realize that these drinks do more to excite than to relieve tension The vasodilator effect of caffeine is not therapeutically useful Equal benefit is obtainable from the use of any other hot drink

Insomnia—Insomnia is probably more a reflection of underlying anxiety than a specific effect of the disease However what may seem simple insomnia may be an early manifestation of heart failure (p 202) *Ideally its treatment consists in the relief of the anxiety*

Insofar as there has developed a vicious cycle in which the fear of not sleeping prevents sleep the assurance that rest may be obtained by relaxation without sleep is useful Empiric rules such as those outlined by one of us for the patients use may prove beneficial Most of these are matters of ordinary common sense Certain patients may be led to a purposeful satisfying and soluble train of thought by application of Jacobsons method of progressive relaxation

When insomnia is a real problem it is wisely met by the use of hypnotic drugs Their recommendation may be prefaced by the explanation that they are not dope for the fear of them is widespread owing partly to misinformation and partly to neurotic resistance The choice is made from the character of the insomnia Difficulty in getting to sleep is countered by a quick acting barbiturate The same drug given on retiring in enteric coating may aid those who wake at cockcrow Alternatively a long acting barbiturate such as phenobarbital or amytal[8] (3/4–1 1/2 gr) may be given an hour before retiring Should tension persist during the day the dose may be repeated once or twice

Certain patients will find chloral hydrate more useful than the barbiturates It is given in 5 10 or 15 gr dosage either in simple solution or in a mixture such as hypertensive mixture It has a

℞	Syr ac hydriot ci	0 48
	Potas bromidi	16 0
	Chloral hydratis	32 0
	Muc acacia	60 0
	Syr aurantii	120 0
	Aq dest. q s. ad	240 0

Sig. 4 cc. once twice or three times a day

rapid action and it may be that its taste ordinarily *objectionable* is sometimes a virtue

The *menopause* is commonly associated with insomnia At least half the women who find this period one of great tension formerly showed neurotic trends which the menopause only exaggerates The underlying neurosis will not be cured by estrogen The tension may

be relieved by minor psychotherapy—witness the age long use of inactive ovarian preparations and of valerian Objective as well as subjective relief is obtained by administration of an estrogen To this end stilbestrol is given orally in a minimal effective dose (0 2–1 mg) daily and, if need be, supplemented by small doses of long acting barbiturates

BIBLIOGRAPHY

AYMAN D AND PRATT J H *Nature of the symptoms associated with essential hypertension* Arch Int Med 47 675 1931

BINGER C ACKERMAN N W COHN A E SCHROEDER H A AND STEELE J M. Personality in Arterial Hypertension (Psychosom Med Monograph VIII 2d series 1944)

——— *A critique of psychotherapy in arterial hypertension* Bull New York Acad Med 21 610 1945

DONNISON C P Civilization and Disease (Baltimore Williams & Wilkins Company 1937)

DUNBAR F Psychosomatic Diagnosis (New York Paul B Hoeber Inc 1943)

GRAHAM J D P High blood pressure after battle Lancet I 239 1945

GRESSEL G C SHOBE F O SASLOW G DUBOIS P H AND SCHROEDER H A Personality factors in arterial hypertension J A M A 140 265 1949

HAMILTON J A Psychopathology of blood pressure Psychosom Med 4 125 1942

JACOBSON E Progressive Relaxation (Chicago University of Chicago Press 1929)

LEVINE M Psychotherapy in Medical Practice (New York The Macmillan Company 1943)

MENNINGER K A Emotional factors in hypertension Bull New York Acad Med 14 198 1938

PAGE I H Hypertension A Manual for Patients (Springfield Ill Charles C Thomas Publisher 1943)

RENNIE T A C The role of personality in certain hypertensive states New England J Med 221 448 1939

RUSKIN A BEARD O W AND SCHAFFER R Blast hypertension Am J Med 4 228 1948

Symposium on hypertension Psychosom Med 1 93 1939

Symposium Abuse of rest J A M A 125 1075 1944

WEISS E *Psychosomatic aspects of hypertension* J A M A 120 1081 1942

——— AND ENGLISH O S Psychosomatic Medicine (Philadelphia W B Saunders Company 1943)

WHEELER E O AND WHITE P D Insomnia due to left ventricular heart failure J A M A 129 1158 1945

SECTION III

8 Circulation in Early Hypertension

I GENERAL CONSIDERATIONS

THIS SECTION (Chapters 8 and 9) portrays the cardiovascular evolution of the disease The vascular pattern is considered under functional and structural aspects The functional changes are thought of as those which sustain the disease and those which result from it The structural aspect includes age-conditioned changes which the vascular tree has usually undergone by the time hypertension has set in and the influence of high arterial pressure on these

Since structure and function cannot be divorced in practice their consideration is combined. After general statements on the mechanism of hypertension and structure of the vascular system as hypertension finds and leaves it the discussion will proceed to the pattern of change in the coronary arteries and myocardium elastic and muscular arteries and arterioles Diagnostic measures and relevant modes of treatment are noted as occasions arise The consideration is limited by the fact that circulation is quantitatively normal in most areas of the body early in the disease The uncertain and highly variable duration of this phase compels the selection of some term other than early hypertension and we therefore consider it as that of *vascular adaptation* The decrescent stages—which *in point of* time are sometimes early—are associated with partial or complete failure of circulation in local areas The local aspects of failing adaptation are considered under the separate headings of vascular

injury in heart brain and kidney The special problems posed by the consideration of renal function demand that the discussion of this area include the process from beginning to end

Mechanism of Hypertension

The basic consideration in essential hypertension is that we deal with a system in which arterial pressure is increased in the systemic circulation but except secondarily not in the pulmonary bed and the right ventricle The increased pressure might in theory result from increased left ventricular output the resistance to flow through its channels of distribution remaining constant Or again it might be due to increased resistance in the systemic channels the output of their pump being constant but the force of its beat increased As it applies to essential hypertension in man the first possibility may be dismissed for cardiac output is not increased but is often slightly decreased The primary characteristic of the process is increased vascular resistance peripheral to the pump This resistance might result from increased viscosity of the blood or from narrowing of the channels through which blood must flow There is no evidence to support the first possibility but a good deal to confirm the second Hypertension then is characterized by increased resistance the result of narrowed channels of blood flow This narrowing might occur variously in large arteries in small arteries and arterioles in capillaries or conceivably on the venous side of the capillaries But since there is neither cyanosis to suggest venous obstruction nor pallor to indicate constriction of the capillaries the resistance cannot rise in either of these sites The narrowed channels are therefore arterial or arteriolar and the process might be diffuse or localized However local arterial constriction or obliteration does not of itself increase arterial pressure nor does even the removal of such large channels as those of the four extremities Indeed with successive experimental restrictions of arterial outflow increased pressure does not appear as the sole result of restricted arterial capacity until the

splanchnic vascular bed is removed from the circulation We may therefore say that essential hypertension is characterized by in creased vascular resistance the result of widespread narrowing of precapillary channels presumably diffuse throughout the body

The locale of the increased arterial resistance may be found by measurements of the extent to which pressure falls in arterial chan nels as the blood travels farther from the heart Normally the mean arterial pressure of 100 mm Hg is decreased by about 30 mm Hg in its passage through arteries to arterioles the blood entering ar terioles at about 70 mm Hg pressure flows into the capillaries at about 30 mm Hg The arterial gradient (100–70) is thus 30 mm Hg and the arteriolar (70–30) 40 mm Hg In hypertension the arterial mean pressure may be 150 mm Hg and arteriolar pressure 120 mm Hg while capillary pressure is still 30 mm. Hg Here then the arterial gradient is normal and the arteriolar gradient increased to 90 mm Hg Since gradient of pressure expresses the resistance to the flow of blood and since only the arteriolar gradient is greatly increased in hypertension it follows that the increased vascular re sistance of hypertension is concentrated in the arterioles

The arterioles are therefore a focus of interest. They are small short vessels whose precise dimensions are matters of dispute among histologists They range in diameter from 20 to 150 millimicrons Their histologic structure is summarized in the statement that the muscular media forms the largest part of the vessel and that its thickness is about half that of the lumen By their extent and num ber their aggregate cross sectional area is nearly 10 times that of the arteries Constriction and relaxation of their muscular walls in re sponse to nervous and humoral stimuli cause them to act as the stopcocks which control the run-off of arterial blood into the capil laries Thus they constitute most of what we mean when we speak of peripheral resistance More than any other factor the state of their musculature determines the resistance to the outflow of blood from arterial channels and the heart

Arterial hypertension as a disease is one expression of an abnormal accentuation of arteriolar resistance The extent to which functional abnormalities of large arteries and particularly of the heart and aorta participate in increasing arterial pressure is a discussion to which we shall return But in this general survey we must turn now to the structural changes which accompany and follow pathologically increased arteriolar resistance

VASCULAR SENESCENCE

The state of the vascular tree at the onset of hypertension forms the structural substrate on which the disease evolves Its character is largely determined by the age at which the disease is fully established and this as we have seen, is commonly in the late thirties and early forties At this time some parts of the vascular system are well advanced in senescence while others commonly remain youthful and capable of a further wide degree of plastic change The changes due to hypertension assume the character of accelerated senescence In this connection it is worth noting that the term senescence (Lat *senesco,* I grow older) does not carry the connotation of established senility (Lat *senilis,* aged) commonly given it Senescent changes occur from the time of conception and even in a world whose advertisers consider youth a virtue no one need be ashamed of growing old

In summarizing circulatory senescence it is useful to consider the cardiovascular system as a unit in which certain areas are specialized in structure and modified in function with advancing maturity, although no one becomes dispensable The system originates in hollowed out cords of mesodermal angioblasts along which rapid waves of peristaltic contraction weakly provide a sluggish stream Later most of the energy of the contractions is localized and the force increased by centering it in wide and muscular portions of the tube As specialization proceeds in this the primitive heart it advances along other lines in other segments Arteries large and

small elastic and muscular arterioles capillaries shunts and veins are differentiated Basically these are all regions of the whole The system is one organ to which one term, such as angion might be applied if its use would obviate the misconception of cardiac dominance which the term cardiovascular seems to convey

The unity of the system is expressed in its structural and functional responses to stimuli for with differences of emphasis these are the same in every zone This uniformity appears in the reactions to age which are present at the onset of hypertension and in their acceleration which follows its persistence

The age-conditioned changes proceed in three phases—maturation maturity and decline They cannot be sharply separated in terms of years since they proceed at different rates in different regions The changes proceed most rapidly in arterial channels and in the heart, probably owing to greater and unremitting physical work although they may assume a similar character in veins With the phase of maturation we have little to do The maturity of arteries is associated with a splitting of intimal elastic tissue which at first seems to increase in amount and then fragments Fragmentation is followed by loss of elastic tissue and its replacement by fibrous tissue so that functionally it is followed by loss of elasticity and beginning decline Because the distending lateral and longitudinal pressure remains the inelastic arteries dilate and elongate and since they are fixed at certain points become tortuous The small channels such as the arterioles are muscular rather than elastic their intimal reaction with onset of decline is an impregnation of subintimal connective tissue with a mixture of protein and lipid which stains characteristically as hyaline This deposit extends inward to encroach on the lumen or outward to invade the media.

Late maturity and early decline are equally associated with regression of elastic and muscular tissue and growth of connective tissue in the heart In the muscle brown pigment is laid down in increasing amounts at the nuclear poles from early decades The

Arterial hypertension as a disease is one expression of an abnormal accentuation of arteriolar resistance The extent to which functional abnormalities of large arteries and particularly of the heart and aorta participate in increasing arterial pressure is a discussion to which we shall return But in this general survey we must turn now to the structural changes which accompany and follow pathologically increased arteriolar resistance

Vascular Senescence

The state of the vascular tree at the onset of hypertension forms the structural substrate on which the disease evolves Its character is largely determined by the age at which the disease is fully established and this as we have seen, is commonly in the late thirties and early forties At this time some parts of the vascular system are well advanced in senescence, while others commonly remain youthful and capable of a further wide degree of plastic change The changes due to hypertension assume the character of accelerated senescence In this connection it is worth noting that the term senescence (Lat, *senesco,* I grow older) does not carry the connotation of established senility (Lat *senilis* aged) commonly given it Senescent changes occur from the time of conception, and even in a world whose advertisers consider youth a virtue no one need be ashamed of growing old

In summarizing circulatory senescence it is useful to consider the cardiovascular system as a unit in which certain areas are specialized in structure and modified in function with advancing maturity although no one becomes dispensable The system originates in hollowed out cords of mesodermal angioblasts along which rapid waves of peristaltic contraction weakly provide a sluggish stream Later most of the energy of the contractions is localized and the force increased by centering it in wide and muscular portions of the tube As specialization proceeds in this the primitive heart, it advances along other lines in other segments Arteries large and

small elastic and muscular arterioles capillaries shunts and veins are differentiated Basically these are all regions of the whole The system is one organ to which one term, such as angion" might be applied if its use would obviate the misconception of cardiac dominance which the term cardiovascular seems to convey

The unity of the system is expressed in its structural and functional responses to stimuli for with differences of emphasis these are the same in every zone This uniformity appears in the reactions to age which are present at the onset of hypertension and in their acceleration which follows its persistence

The age-conditioned changes proceed in three phases—maturation, maturity and decline They cannot be sharply separated in terms of years since they proceed at different rates in different regions The changes proceed most rapidly in arterial channels and in the heart, probably owing to greater and unremitting physical work although they may assume a similar character in veins With the phase of maturation we have little to do The maturity of arteries is associated with a splitting of intimal elastic tissue which at first seems to increase in amount and then fragments Fragmentation is followed by loss of elastic tissue and its replacement by fibrous tissue so that functionally it is followed by loss of elasticity and beginning decline Because the distending lateral and longitudinal pressure remains the inelastic arteries dilate and elongate and, since they are fixed at certain points become tortuous The small channels such as the arterioles are muscular rather than elastic their intimal reaction with onset of decline is an impregnation of subintimal connective tissue with a mixture of protein and lipid which stains characteristically as hyaline This deposit extends inward to encroach on the lumen or outward to invade the media.

Late maturity and early decline are equally associated with regression of elastic and muscular tissue and growth of connective tissue in the heart. In the muscle brown pigment is laid down in increasing amounts at the nuclear poles from early decades The

muscular striations disappear in the path of advancing deposition

The phase of established decline is termed senile fibrosis It results in decreased functional capacity of all tissues but does not of itself place life in instant jeopardy However since fibrous subendothelial tissue is highly susceptible to atherosclerosis the process though not necessarily an obstacle to function, is one onto which disease is easily grafted

Atherosclerosis

That atherosclerosis is a disease not casually to be dismissed as a problem of aging —as if a problem of aging were dismissible— is indicated by the scatter of its occurrence in age and disease groups and is more particularly attested by its rarity in animals other than man The process begins in the matrix of decrescent thickened sub endothelial connective tissue Through this course an increasing number of minute capillary channels Deposits of lipid either by imbibition from plasma or by conveyance in macrophages appear as fatty streaks which phagocytosis may remove when the intima is still young and thin But as age coarsens and thickens its texture the deposits are not scavenged away The fatty particles coalesce and around them forms a condensed hull of fibrous tissue The localization of these deposits is not unexpectedly most intense in arteries of predominantly elastic character Here intimal changes are most profound especially at sites of acute branching where mechanical stresses are most intense and newly formed vascular channels most abundant Some protection seems to be conferred by the arteries being enveloped in a supporting tissue Here and there around the lipid deposit the collagen weakens and begins to necrose so that the lipids aggregate into pools and *puddles of mush* (Gr *atheros* mush) In other areas the fat is mostly removed in macrophages and a thickened fibrous scar marks its wake As necrosis begins in the base of the lesion it destroys first the fenestrated barrier of elastic tissue then the scar which replaces it until the process

advances into the media and repeats itself When the film of scar over the luminal surface is liquefied and endothelium necrosed the atheroma is naked to the current of blood and a thrombus forms in the ulcer Hemorrhage from vasa vasorum at the base of the lesion may precipitate endothelial loss

These two processes senile decrescent fibrosis and atherosclerosis are commonly present in some parts of the vascular system when hypertension is thrust upon it. The fibrotic element dilates and lengthens the vessels but does not obstruct them the atherosclerotic element may impinge on the lumen or weaken the media As the channel narrows or endothelium is lost from the surface of an atheroma the peril of thrombotic occlusion arises

Hypertensive Vascular Disease

The vascular abnormalities of hypertension fall *in two groups* first those which sustain the process and later those which result from it The first order of change is functional and reactive It is concentrated in maintenance of a nearly normal circulation through tissue capillaries in the face of increased arteriolar resistance To this end the heart beats more vigorously arterial pressure rises and cardiac output is maintained. In this the phase of adaptation there are therefore no angiogenic symptoms of tissue ischemia and only scant physical signs of local change The phase of failing adjustment is evidenced by signs of wear and tear in affected zones of the circulatory system

The underlying abnormality to which the heart and arterial vessels adapt at first is overwork Loss of adaptation implies a failure to maintain the pace The responses to overwork of even such complicated structures as cardiac and vascular tissues are few They can not like their possessors quit work get drunk or enter politics Rather they must proceed although at an accelerated rate and with added hazards in much the direction they were going when the disease had its onset Hypertension speeds the senescence of arteries

muscular striations disappear in the path of advancing deposition

The phase of established decline is termed *senile fibrosis* It results in decreased functional capacity of all tissues but does not of itself place life in instant jeopardy However since fibrous subendothelial tissue is highly susceptible to atherosclerosis the process though not necessarily an obstacle to function is one onto which disease is easily grafted

ATHEROSCLEROSIS

That atherosclerosis is a disease not casually to be dismissed as a problem of aging —as if a problem of aging were dismissible— is indicated by the scatter of its occurrence in age and disease groups and is more particularly attested by its rarity in animals other than man The process begins in the matrix of decrescent thickened subendothelial connective tissue Through this course an increasing number of minute capillary channels Deposits of lipid either by imbibition from plasma or by conveyance in macrophages appear as fatty streaks which phagocytosis may remove when the intima is still young and thin But as age coarsens and thickens its texture the deposits are not scavenged away The fatty particles coalesce and around them forms a condensed hull of fibrous tissue The localization of these deposits is not unexpectedly most intense in arteries of predominantly elastic character Here intimal changes are most profound especially at sites of acute branching where mechanical stresses are most intense and newly formed vascular channels most abundant Some protection seems to be conferred by the arteries being enveloped in a supporting tissue Here and there around the lipid deposit the collagen weakens and begins to necrose so that the lipids aggregate into pools and puddles of mush (Gr *atheros* mush) *In other areas the fat is mostly removed in macrophages* and a thickened fibrous scar marks its wake As necrosis begins in the base of the lesion it destroys first the fenestrated barrier of elastic tissue then the scar which replaces it until the process

them and goes on to their finer branches as they weave basket like into the spiraled muscle bands of the myocardium But systolic tension of ventricular muscle slows the onward flow into the deep myocardial capillaries In diastole the relaxing myocardium lessens the resistance to flow through terminal vessels and blood flows steadily through under the gradually decreasing diastolic aortic pressure A cyclic onward flow is thus maintained in both phases of the heart s beat, but the volume flow and effectiveness of tissue perfusion are probably greater in diastole increased aortic diastolic pressure in the absence of coronary vasoconstriction causes a parallel increase in diastolic blood flow Apart from the mechanical factors of systolic and diastolic pressures which determine coronary blood flow the autonomic nerves of the vessels may cause them to dilate or constrict Further humoral stimuli (adrenaline angiotonin) may alter their set locally formed substances derived from the normal metabolism of muscle (CO_2 adenine) may dilate them Histamine and other substances abnormally liberated at the site of muscle necrosis may do the same Coronary flow is thus adjusted by aortic pressure and cardiac systolic effort on the one hand, and by reflex and chemical stimuli which tend to vary the flow of blood to meet myocardial requirements on the other

This adjustment, though exact over narrow ranges of effort is not all-compelling Thus during strenuous exercise when the work of the body and cardiac output may be increased about tenfold coronary blood flow increases only three or fourfold. The great capacity of the somatic muscles for briefly sustained energy output is largely due to the faculty of creating an oxygen debt. Temporarily their performance may exceed both their blood flow and their oxygen supply This the myocardium cannot do A result is that even in normal hearts severe exertion makes the gap between physical requirements of myocardial muscle and the possibility of their fulfilment a narrow one The relation between reduced capacity for exercise in hypertension and coronary artery insufficiency is thus appar

toward premature senility Senile fibrosis is exaggerated, atherosclerosis becomes more intense and, *since arterioles are the focus of* much of the increased effort they regress at an extraordinarily rapid pace and desert the usual order and at times the character of their change

II THE CORONARY CIRCULATION

One logical procedure in consideration of hypertension which, *although arising in arterioles reflects itself in the whole circulation* is to travel with the blood from the heart much in the manner prescribed by Virchow for orderly autopsies The first avenue of distribution of blood is formed by the coronary circulation These arteries, *normally* two right and left, arise in ostia at the base of the aorta and, passing to their distributions, circle the top of the heart like a coronet Under basal conditions the volume flow of blood through the two of them equals some 5 or 10 per cent of the cardiac output Possibly two thirds of the roughly *200* cc per minute of basal coronary blood flow passes through the larger left coronary artery to the larger muscle mass of the left ventricle Although there is a good deal of anatomic variation in their distribution and sometimes an accessory artery at the origin which replaces the anterior descending branch of the left coronary artery it is a working rule that the arteries nourish their ipsilateral ventricles As a result, most of the left ventricular muscle and the neuromuscular tissue as well receives its blood supply from the left coronary artery, the right coronary nourishes most of the right ventricle in about 60 per cent of hearts the sinoauricular node and in some 80 per cent the sinoventricular node also In roughly 5 per cent of hearts *all* neuromuscular tissue and in 10 per cent all but the sinoauricular node is supplied by the left coronary artery

During systole the sharp rise of aortic pressure forces blood into the main coronary arteries The blood passes through and distends

would have to be considered main channels However when obstruction of a coronary artery or of one of its branches has greatly reduced pressure in some distal branch blood may flow from a small collateral of higher pressure into the area of lower pressure As the collateral flow persists it is increased by chemical vasodilators and possibly reflexly so that its volume rises the channel enlarges and the vessels walls become more fitted to their task The effectiveness of collateral perfusion is thus increased until some point of equilibrium is reached In this connection the increase with age in the size and visible number of anastomoses of the right and left coronaries visualized by some as a sort of teleologic preparation for the onset of left coronary arterial occlusion is functionally ineffective As we have seen the diameter of most arteries including coronary collaterals increases with senile fibrosis Functionally *coronary occlusion* is more frequently fatal in old age Some of the increased number of channels probably arise from insufficient perfusion and pressure in branches of the left coronary artery

Coronary Circulation in Hypertension

In considering the *coronary circulation* in hypertension we are faced with the fact that its arteries *more than* any other branch of the aorta are prone to changes of aging

The general classification of arteries into muscular and elastic *types must* be noted In general peripheral arteries are *muscular* and subject without much loss of function to deposition of calcium in their media Central *arteries* typically the aorta are predominantly elastic rather than muscular and as such are predisposed to atherosclerosis This classification like many another has an unhappy way of limping just when it could be useful for the coronaries muscular *arteries in* youth become in some *measure* elastic and in large *measure* fibrous in middle age which like life is reported to begin at 40 *Senescent* changes appear before birth and are always more advanced in the left than in the right artery so that

ent for here the basal effort is already large In this connection, too there should be noted the increased coronary blood flow which normally accompanies digestion and the vasoconstriction which follows painful stimulation or distention of hollow viscera In man whirling emotions of rage or anxiety may replace the experimentalist s *painful stimuli in reducing coronary flow*

Collateral Channels

The most significant thing that coronary arteries can do is to cease to fulfil their normal function as the result of partial or complete occlusion As a result a good deal of effort has been applied to the study of collateral channels of myocardial blood flow The aim has been to answer the question Are coronary arteries end arteries? The search has perhaps suffered from an initial failure to define its terms Thus some view as an end artery any artery whose obstruction causes infarction of the tissue it supplies, others maintain that *true infarction is inconceivable in the absence of some collateral* channels But as regards the intent of the question the answer too often given by presence of coronary occlusion and myocardial infarction at autopsy is that obstruction of a major coronary artery causes death of tissue beyond Experimental ligation of such a vessel is followed in about one minute by cyanosis and failure of mechanical and electrical systole in part of the area supplied by that vessel The conclusive studies of Prinzmetal and co workers establish the presence of freely open collaterals of at least arteriolar size But as they point out these vessels do not provide adequate perfusion after obstruction of major channels The size of these intercoronary *channels is increased in hearts whose coronary arteries have* been obstructed or narrowed

The consideration which *underlies these or any arterial collaterals* is that blood *will only flow* into vessels *of lower pressure* Were they in their normal state large vessels containing blood under sufficient pressure to equalize that of the main channels they

would have to be considered main channels However when obstruction of a coronary artery or of one of its branches has greatly reduced pressure in some distal branch blood may flow from a small collateral of higher pressure into the area of lower pressure As the collateral flow persists it is increased by chemical vasodilators and possibly reflexly so that its volume rises the channel enlarges and the vessels walls become more fitted to their task. The effectiveness of collateral perfusion is thus increased until some point of equilibrium is reached. In this connection the increase with age in the size and visible number of anastomoses of the right and left coronaries visualized by some as a sort of teleologic preparation for the onset of left coronary arterial occlusion is functionally ineffective As we have seen the diameter of most arteries including coronary collaterals increases with senile fibrosis Functionally coronary occlusion is more frequently fatal in old age Some of the increased number of channels probably arise from insufficient perfusion and pressure in branches of the left coronary artery

Coronary Circulation in Hypertension

In considering the coronary circulation in hypertension we are faced with the fact that its arteries more than any other branch of the aorta are prone to changes of aging

The general classification of arteries into *muscular* and *elastic* types must be noted In general peripheral arteries are muscular and subject without much loss of function, to deposition of calcium in their media Central arteries typically the aorta, are predominantly elastic rather than muscular and as such are predisposed to atherosclerosis This classification like many another has an unhappy way of limping just when it could be useful for the coronaries muscular arteries in youth become in some measure elastic and in large measure *fibrous* in middle age which like life is reported to begin at 40 Senescent changes appear before birth and are always more advanced in the left than in the right artery so that

structurally the left coronary, notably its anterior descending branch, is 10–20 years older than the right The first change splits the internal elastic lamina into two layers so that the thickness of the intima increases although in childhood it does not commonly exceed that of the media In the second and third decades a layer of connective tissue forms in the intima under the endothelium and by the fourth decade the thickness of the intimal layer may many times exceed that of the muscle, the *preponderance of intimal tissue is collagenous* rather than elastic About this time the elastic layer begins to fragment and break into short and ineffective strands Thus, three phases of change may be recognized (Aschoff) (1) a period of accelerated growth, especially of the left coronary artery as it keeps pace with the growth of the left ventricle, (2) a period of established development, and (3) a phase of regression with change from elastic to connective tissue

Coronary Atherosclerosis

Coronary atherosclerosis appears as senescence develops and according to some observers, earlier in America than in Europe It is so common on both continents that some view it as one of the phenomena of arterial regression

Here as elsewhere it begins with fatty subendothelial deposits which extend to form atheromatous plaques They seldom encroach on the lumen until the third decade and at this time are more often present only in the left coronary and here usually just before the branching of the anterior descending artery In time plaques appear elsewhere usually on the cardiac surface of the artery and near a *point of branching advancing slowly* into smaller branches and eventually, into the right coronary The onset of atherosclerosis is enhanced by intimal thickening and a high degree of intimal thickening in middle life is characteristic of the coronary arteries

It is therefore not surprising that coronary atherosclerosis is often reflected in manifest disease it is surprising that the relation

ship was not recognized before John Hunter died and that frank coronary affliction is not more frequent. Unfortunately for precision terms such as sclerosis and even atheroma have different meanings to different observers Degrees of change which one will note as convincing evidence of abnormality another may disregard Thus while some consider atheroma of the coronaries almost constantly present after the fifth decade others find it only common However this may be it is upon this play of arterial change that hypertension is imposed and thus most commonly at a time when hyperplastic connective tissue has formed as a lodging place for atheroma

EFFECTS OF HYPERTENSION

The first change which hypertension causes in the coronary circulation is an increase of systolic and diastolic pressure Because of the increased systolic myocardial effort there is probably little change in systolic blood flow and in diastole the tendency to increased flow may be countered by increased vascular resistance With marked hypertension it may be that the volume of systolic flow is locally decreased in the innermost bands of muscle

Hypertension also seems to accelerate the lethal progression of senescent changes in the arteries and arterioles although uncertainties of definition make it difficult to determine the precise degree of acceleration it induces Fahr from data of Bell and Clawson was led to the view that arteriosclerosis of the coronary arteries is present in 90 per cent of hypertensive patients seen at autopsy an incidence much higher than that in nonhypertensives of similar age groups although common among normotensives at the age of 70 or over An experimental demonstration of the influence of hypertension on coronary arterial disease is made by nature Coronary atherosclerosis is rare among normotensive females in younger age groups This relative insusceptibility all but disappears in the presence of hypertension

Before considering the tissues they perfuse we must turn from

the larger arterial branches to the small arteries and arterioles of the coronary bed The smaller branches of the arteries come off almost at right angles as they enter the muscle and therefore are not in the streamline of pressure They are also closely invested and supported by the myocardium Even though severe changes appear in the main arteries with aging the small coronary arteries and arterioles show at most only slight intimal hyalinization In hypertension like other arterioles they are constricted and their media hypertrophic Still *they almost alone among small arterial channels fail to show the* severe regressive intimal changes which are the fate of such vessels elsewhere during the progress of hypertension Thus the general rule that hypertension specifically affects and injures arterioles does not apply in the myocardium Here the injury is usually either arterial or myocardial

III THE MYOCARDIUM

While we assign to arteriolar vasoconstriction a primary role in the pathogenesis of hypertension we recognize that no increase of pressure can follow an increased resistance unless there develops some increase in the force of the heart s beat Since the arteriolar vasoconstriction is systemic and not pulmonary the augmented force of the heart s beat is lopsided It expresses itself as a provision to the blood of greater kinetic and potential energy as it leaves the left ventricle The result of this activity by the left ventricle is increased systolic pressure an exaggerated rebound of the elastic vessels increases diastolic pressure and forces the blood through constricted arterioles at about a normal rate in diastole The perfusion of the body tissues is maintained

Teleologically cardiac augmentation in hypertension is useful and life saving Several factors participate in its onset and continuance We can consider the probability that nervous impulses are

released from the vasomotor center possibly because it is threatened with ischemia in some sensitive endpiece Further as we shall see when the renal pressor system is active its effector agent angiotonin directly stimulates cardiac muscle or itself affects the vasomotor centers But if we visualize that hypothetical moment at which hypertension had its onset and peripheral resistance first increased we can see that in diastole a residue of blood would remain in the left ventricle Diastolic size of the ventricle would be increased and the muscle fibers accordingly stretched Cardiac muscle in the pattern of Starling s law responds to increased stretch by increased contraction and, in succeeding contractions resists stretch Cardiac output is thus maintained at or near the level which existed before peripheral resistance had increased diastolic volume In this manner hypertension may be considered as beginning in compensated cardiac dilatation to which mechanism other myocardial stimuli may be added

The augmented cardiac effort of hypertension implies an increase in cardiac work since it implies the transfer of a mass the cardiac output, through space against a greater than normal resistance Mechanical models or physiologic preparations such as heart lung provide direct means of measuring cardiac work at such different levels of resistance These measurements cannot be directly transferred to the patient. Indirectly it may be shown that cardiac work in hypertension increases roughly in proportion to the increase of systolic arterial pressure or may exceed this ratio Thus an increase of pressure from 120 80 to 240/130 mm Hg doubles the work of the heart. The physician can at times estimate the energy released in cardiac systole by palpation of the apex beat and auscultation of the apical first and aortic second sounds True some of the accentuation of beat and sound in hypertension is the result of rotation of the apex toward the chest wall during left ventricular hypertrophy which imparts an added intensity of apical throb

Myocardial Contraction

The increase in cardiac work demands from the muscle fibers a greater than normal conversion of the chemical energy of muscular metabolism into the potential and kinetic energy of contraction and systolic discharge The metabolic demand of the heart is therefore increased as cardiac work increases, i e, roughly as systolic pressure rises The physical energy of contraction is derived from shortening of linked chains of muscle protein (myosin) Its chemical energy is derived from oxidation of glucose lactic and other fatty acids It may be dependent on the glycogen stores of the muscle Ultimately, by transfers of oxygen and hydrogen and enzymatic decomposition of the substrates to carbon dioxide and water chemical energy is released and partly utilized in recomposing the two esters of phosphoric acid, phosphocreatine and adenylpyrophosphate, whose hydrolysis more directly provides the muscle protein with energy Curiously the contracting substance myosin is the enzyme which catalyzed by calcium ion causes the breakdown of adenylpyrophosphate to provide the energy which contracts myosin The product of this decomposition, adenylic acid is again bound to phosphoric acid as the wave of contraction passes off Since the energy of contraction demands the inflow of blood with a supply of nutrients and of oxygen, it is of interest that adenylic acid a product of contraction, is a powerful dilator of coronary vessels Thus at the muscle cell itself there may be provided one of the controls which increase coronary blood flow to meet the increased metabolic demands of hypertension

The earliest means of adaptation to hypertension namely, increased diastolic volume with stretching and consequent increased contraction of muscle fibers we have already noted Later adaptation is outwardly manifest in two changes either one of which may predominate in individual patients The more common is hypertrophy and hyperplasia of the muscle cells a process in which the

cells increase both in individual size and in aggregate number so that the mass of cardiac muscle is enlarged. A deeper stronger cham ber is thus provided in the pump and cardiac output is maintained. Another avenue of adaptation and one which clinically seems less effective, is the onset of tachycardia A rapid heart rate raises the pressure at which blood is discharged and may maintain the output against increased resistance but only by encroaching on myocardial reserve

HYPERTROPHY

The nature and origin of hypertrophy is still a vexed and puz zling question and one which carries us into a consideration of the late and damaging end results of hypertension

The analogy with the blacksmith s biceps is obvious but disap pointing it is not at all certain that increased cardiac work alone accounts for hypertrophy Even granting work as the ultimate stim ulus to the growth of cardiac muscle questions regarding the nature of the proximal stimuli which act directly on the cells remain Trophic nervous influences are not readily excluded.

Chemical stimuli for example the metabolic products of in creased work and the hyperemia which must accompany it, may operate in part. The most probable stimulus is that which first caused the fibers to respond with increased effort i e their stretch ing by an actual or potential increase of diastolic cardiac volume Since the heart as a whole and more so the left ventricle increases in size with growth it may be argued that hypertrophy is a physi ologic process Conviction is given the argument by the demonstra tion that myocardial fibers increase in number and diameter The fibers of the hypertrophied heart are like those of the normal adult, still supplied by a capillary The deviation of hypertrophy from the normal pattern lies in the fact that the excessively large muscle fiber is nourished by a capillary of only moderate area Because of this disproportion the rapid transfer of nutrients and metabolites is

slowed and function is jeopardized Briefly the process is one in which the hypertrophying myocardial fiber outgrows its capillary

If this is true of the capillaries which distribute the blood it is in some degree true of the arteries which bring the blood Normal cardiac growth and maturation are accompanied by corresponding increases in size and capacity of the coronary arteries during hypertrophy the arteries do *not* grow but as we have seen usually undergo accelerated regressive and occlusive change The hypertrophied heart then is either actually or potentially ischemic Ischemia may turn on itself to cause hypertrophy for as ischemia injures the contractile power of the muscle it allows stretching and this despite marginal nutrition stimulates growth Thus hypertrophy may develop during attacks of cardiac failure or when the heart is perfused *with venous blood from an abnormal origin of the coronary arteries* in the pulmonary In this manner there is created in hypertension a vicious circle of hypertrophy in which the adaptive response injures the nutrition of the muscle and the perverted stimulus of stretch causes growth toward weakness rather than toward strength

Myocardial Efficiency

*In hypertension we have at the outset to deal with a heart work*ing under a disadvantage at more than a normal pace for its load of work is increased and its blood supply is diminishing The situation is analogous to that of a motor whose load is increased which cannot be temporarily replaced for repair and which once stalled is of no further use The heart's tolerance of these injuries depends on the efficiency with which it continues to work efficiency being un*derstood* as the amount of work done per unit of energy consumed The isolated mammalian heart has an efficiency of about 10 per cent (steam engine 10 electric motor 50) Data for such calculations are not available for intact animals or human beings However an indirect approach permits an estimate of the economy of cardiac effort a value which expresses *the ease with which the heart meets*

changing demands for work Comparison of values for this index in normotensives and hypertensives indicates that the heart in uncomplicated hypertension does its larger share of work with less than a proportional expenditure of effort. The heart of the hypertensive is at first *more* rather than less efficient It has it seems adapted to increased work along the pattern of increased efficiency adopted by the trained athlete or the experienced industrial worker But while it is a more efficient converter of energy two disadvantages have been imposed on it. One is that the heart has reduced its margin of capacity for a further increase in work by setting the basal level in what before the onset of hypertension was the zone of cardiac reserve Another and more serious disadvantage is that increased work however efficient, brings increased wear and a greater likelihood of early breakdown The accumulated effects of tachycardia arterial insufficiency capillary inadequacy and loss of myocardial fiber here and there add hidden loads These ultimately *reduce the level* of efficiency below the normal so that the heart *fails* prematurely The heart cannot eat its cake and have it too But during the phase of adjustment to hypertension it eats a little cake Added to these unavoidable tolls of the hypertensive process is the fact that anxiety so common among patients with hypertension has pronounced effects in whipping up the output of the heart

IV THE ELASTIC ARTERIES

The elastic arteries should be thought of together with the heart because they are usually examined at the same time and because their disorders mimic those of heart disease

These arteries whose walls are composed predominantly of elastic fibers are the aorta pulmonary innominate and subclavian arteries and the proximal portion of the common carotids In them as elsewhere structure is the *mirror* of function The elastic tissue of their walls permits them to expand like elastic bellows and to

slowed and function is jeopardized Briefly the process is one in which the hypertrophying myocardial fiber outgrows its capillary

If this is true of the capillaries which distribute the blood it is in some degree true of the arteries which bring the blood Normal cardiac growth and maturation are accompanied by corresponding increases in size and capacity of the coronary arteries during hypertrophy the arteries do not grow but as we have seen usually undergo accelerated regressive and occlusive change The hypertrophied heart then is either actually or potentially ischemic Ischemia may turn on itself to cause hypertrophy, for as ischemia injures the contractile power of the muscle it allows stretching and this despite marginal nutrition stimulates growth Thus hypertrophy may develop during attacks of cardiac failure or when the heart is perfused with venous blood from an abnormal origin of the coronary arteries in the pulmonary In this manner there is created in hypertension a vicious circle of hypertrophy in which the adaptive response injures the nutrition of the muscle and the perverted stimulus of stretch causes growth toward weakness rather than toward strength

MYOCARDIAL EFFICIENCY

In hypertension we have at the outset to deal with a heart working under a disadvantage at more than a normal pace for its load of work is increased and its blood supply is diminishing The situation is analogous to that of a motor whose load is increased which cannot be temporarily replaced for repair and which once stilled is of no further use The heart s tolerance of these injuries depends on the efficiency with which it continues to work efficiency being understood as the amount of work done per unit of energy consumed The isolated mammalian heart has an efficiency of about 10 per cent (steam engine 10 electric motor 50) Data for such calculations are not available for intact animals or human beings However an indirect approach permits an estimate of the economy of cardiac effort a value which expresses the ease with which the heart meets

volume Thus if aortic dilatation and loss of total elasticity proceed at equal pace systolic pressure may remain at normal levels while diastolic pressure tends to fall But if lost elasticity exceeds distention systolic pressure rises and the wide pulse pattern of senile hypertension is established.

These changes of senile fibrosis are not themselves very harmful However in elastic arteries as in the coronaries a thickening intima provides a lodging place for atherosclerotic deposits Aortic atherosclerosis is therefore common among normotensives at the fourth and fifth decades It develops in a fairly uniform pattern being at first evident and later most severe in the abdominal aorta then at the base of the ascending aorta and later in the descending aorta at the sites of branching The atherosclerotic plaques at first present only in the intima extend in time into the media and weaken the wall. An accelerated elastic regression is the presumptive basis for cystic degeneration of the media (p 110) In contrast with the process in the coronary arteries the intimal plaques do not encroach seriously on the relatively large lumen of the vessel

EFFECTS OF HYPERTENSION

In hypertension the earliest change produced in the aorta is probably a contraction of its scant muscular tissue This would decrease the volume of the storage reservoir and thus increase systolic pressure The contribution of aortic constriction to increased arterial pressure is not known In some patients whose peripheral resistance is not increased in proportion to the increase of arterial pressure it may be important. But in most patients it is countered by aortic dilatation due to fibrosis and tensile stretching Thus concern rests more with the effects of hypertension on elastic vessels than with their functions as causal agents

These effects may be summarized in the statement that hypertension accelerates the progress of senescence and speeds the formation of atherosclerosis so that elastic vessels of the hypertensive are

hold a large part of the blood which enters them in systole so that peripheral arteries are spared a sudden increase in pressure and rise in rate of blood flow As pressure falls in diastole, the elastic walls rebound like springs and force the blood on A uniform speed of peripheral blood flow is thus maintained In this function of systolic storage and diastolic discharge the aorta, because it is largest and nearest the heart, is the most significant It is also the most commonly diseased

SENESCENCE

Elastic tissue the vital rubber as Gideon Wells called it wears and, with the passage of time and effort, comes to a point where it does not replace itself Some have hypothesized that this tissue loses its growing power at about 60 years of age whereas connective tissue can reproduce itself into senility Whether or not this concept is valid it has value in considering the life story of elastic arteries *Their age changes are not unlike those of the coronary intima* In the infant s aorta the elastica interna splits and subendothelial fibrous tissue forms This elastic splitting continues outward into the sparsely muscular media until with the passage of time, elastic tissue is lost and fibrous tissue replaces it The vessel then begins to lose the quality of elasticity, so that it distends less easily in systole and fails to restore its volume in diastole As a result of lateral pressure and weakened circular elastic bands the aorta increases in cross section Because of longitudinal pressure and disrupted longitudinal bands it also increases in length and having fixed points becomes tortuous

With decreasing elasticity goes impairment of the function of alternate storage and discharge of blood Since the systolic volume of blood cannot quickly be received elsewhere systolic arterial pressure tends to rise and since elastic rebound is diminished diastolic pressure usually falls If dilatation is marked even a slight ability *to stretch in systole may permit a considerable increase in storage*

and that although the capacity of such patients for ordinary work is not decreased their vital capacity is commonly reduced from a normal 2 500 cc per square meter of body surface to 1 900 cc This increased pulmonary blood volume may express a partial failure of left ventricular adaptation to the strain of increased pressure or as seems more likely an increased effort of the right ventricular muscle which throws blood into an easily distended system of channels

V PERIPHERAL VESSELS

Blood leaves the storage bed of the elastic arteries to enter vessels whose function is to channel its distribution Nervous and humoral agents modify the volume of this distribution according to tissue need and systemic reaction The walls of the distributing channels are therefore predominantly muscular The blood enters some of them at streamlined angles which neither greatly disturb the smoothness of flow nor distort the mural structure Such vessels the iliacs below carotids and subclavians above show a *transition* from elastic to muscular type Visceral aortic branches differ in that they are short the angle of their exit is acute the stream is turbulent and the change from elastic to muscular tissue is abrupt The acute branchings are sites of predilection for atherosclerotic deposits which therefore are seen here early

Muscular Arteries

The radial is a typical muscular artery and also the artery with which the physician is most familiar Its wall is composed largely of muscle cells the intima is thin and the elastic tissue largely segregated in slender sheets The wall is richly innervated and highly responsive to nervous influence so that spasm spreads readily along it Indeed spasm of its digital branches of distribution seems to underlie the phenomenon of dead fingers Possibly other muscular

old before their time Here note should be made of the variable resistance of the vital rubber to age and wear and this not only between individuals but also between arteries *Thus there is no necessary* correlation between the severity of aortic and coronary arteriosclerosis in the same patient although the two processes usually advance together

A common result of hypertension is that the aorta dilates and becomes elongated so that its pulsation is apparent in the suprasternal fossa The innominate artery—and this more commonly in females—may dilate and present as a mass beneath the sternocleidomastoid muscle *Ultimately* the accidents of serious disease may involve these vessels particularly the aorta in partial or complete rupture

The Pulmonary Circulation

Essential hypertension at its outset is from the heart's point of view lopsided for it arises in the circulation of the left and not that of the right ventricle Pulmonary hypertension when it occurs in essential hypertension is a result either of left ventricular failure or of obstructive pulmonary arterial disease If we pose the question why is the pulmonary circulation spared the stimulus which affects the systemic circulation the answer is that probably it is not spared the whip but rather fails to respond to it

Pulmonary arterial pressure is normally low about 30/10 mm Hg, the arterioles of the lung are not highly muscular structures like those of the peripheral circulation the power of the right ventricle is much less than that of the left Thus a vasoconstrictor stimulus which would greatly increase systemic arterial pressure may cause little or no change in the pulmonary circuit

Measurements of pulmonary circulation time in uncomplicated cases of essential hypertension indicate that there is no retardation of blood flow *Weiss and Ellis obtained evidence that the lungs of* hypertensive patients contain more than the normal volume of blood

and that although the capacity of such patients for ordinary work is not decreased their vital capacity is commonly reduced from a normal 2 500 cc per square meter of body surface to 1 900 cc This increased pulmonary blood volume may express a partial failure of left ventricular adaptation to the strain of increased pressure or as seems more likely an increased effort of the right ventricular muscle which throws blood into an easily distended system of channels

V PERIPHERAL VESSELS

Blood leaves the storage bed of the elastic arteries to enter vessels whose function is to channel its distribution Nervous and humoral agents modify the volume of this distribution according to tissue need and systemic reaction The walls of the distributing channels are therefore predominantly muscular The blood enters some of them at streamlined angles which neither greatly disturb the smoothness of flow nor distort the mural structure Such vessels the iliacs below carotids and subclavians above show a transition from elastic to muscular type Visceral aortic branches differ *in* that they are short the angle of their exit is acute the *stream* is turbulent and the change from elastic to muscular tissue is abrupt The acute branchings are sites of predilection for atherosclerotic deposits which therefore are seen here early

MUSCULAR ARTERIES

The radial is a typical muscular artery and also the artery with which the physician is most familiar Its wall is composed largely of muscle cells the intima is thin and the elastic tissue largely segregated in slender sheets The wall is richly innervated and highly responsive to nervous influence so that spasm spreads readily along it. Indeed, spasm of its digital branches of distribution seems to underlie the phenomenon of dead fingers Possibly other muscular

old before their time Here note should be made of the variable resistance of the vital rubber to age and wear, and this not only between individuals but also between arteries Thus there is no necessary correlation between the severity of aortic and coronary arteriosclerosis in the same patient although the two processes usually advance together

A common result of hypertension is that the aorta dilates and becomes elongated so that its pulsation is apparent in the suprasternal fossa The innominate artery—and this more commonly in females—may dilate and present as a mass beneath the sternocleidomastoid muscle Ultimately the accidents of serious disease may involve these vessels, particularly the aorta in partial or complete rupture

The Pulmonary Circulation

Essential hypertension at its outset is from the heart s point of view lopsided for it arises in the circulation of the left and not that of the right ventricle Pulmonary hypertension when it occurs in essential hypertension is a result either of left ventricular failure or of obstructive pulmonary arterial disease If we pose the question why is the pulmonary circulation spared the stimulus which affects the systemic circulation the answer is that probably it is not spared the whip but rather fails to respond to it

Pulmonary arterial pressure is normally low about 30/10 mm Hg the arterioles of the lung are not highly muscular structures like those of the peripheral circulation the power of the right ventricle is much less than that of the left Thus a vasoconstrictor stimulus which would greatly increase systemic arterial pressure may cause little or no change in the pulmonary circuit

Measurements of pulmonary circulation time in uncomplicated cases of essential hypertension indicate that there is no retardation of blood flow Weiss and Ellis obtained evidence that the lungs of hypertensive patients contain more than the normal volume of blood

Arterioles and Small Arteries

The state of small arteries and arterioles is especially significant In them arise the increased peripheral resistance that characterizes essential hypertension the extracardiac disabilities incident to the disease and the preponderance of its histologic changes

Since these small vessels are composed almost wholly of muscle muscular hypertrophy is the ordinary concomitant of hypertension and fibrosis here as in the heart its sequel Thus the characteristic change of hypertension is medial But, as in larger vessels changes of senescence concentrate in the intima Here it begins with splitting and increase of elastic tissue and subsequent deposition of hyaline The hyaline material deposits eccentrically and in irregular segmental fashion As the process advances it extends into the media and replaces it and into the lumen which it partially obstructs Such severe hyalinization in senescence is in normotensives limited to spleen and pancreas In somewhat larger vessels intermediate between arterioles and small arteries severe hyalinization apparently irritates the endothelium causing it to proliferate into the lumen. The sequence of these intimal changes represents involutional arteriosclerosis and atherosclerosis as they are modified in appearance in minute vessels This interpretation is confirmed by the fact that like atherosclerosis hypertension ordinarily causes these changes not to assume a new character but to be accelerated and diffused

The accelerated intimal and medial arteriolar regressions due to hypertension combine to thicken the wall of the arteriole so that from a thickness of about half that of the lumen it becomes a more conspicuous part of the vessel This increase of the ratio of wall to lumen may be estimated by averages of measurements made from arterioles in blocks of tissue (Table 6) From these values it will be seen that in hypertension the severest changes of this sort occur in spleen and kidney and the least in the heart. Further in the spleen although increased by hypertension the phenomenon is found in

arteries may be similarly affected, so that similar neurogenic spasm may underlie some irregularly occurring gastrointestinal complaints of hypertensive patients These spasms may appear in the absence of hypertension They are evidences of vasomotor dysfunction and not part of hypertension as such

As the radial artery ages, the course of its change is an attenuation of that described in the coronary arteries Splitting of the elastic lamina does not begin until age 20 or 30 Subendothelial deposition of fibrous tissue is delayed until the fifth decade and never *reaches the degree concurrently present in the coronaries In fact, the* thickest radial artery *of the man of 65 years or more is comparable* to the coronary artery of the youth of 20 Atherosclerosis when it appears in this or similar vessels, is neither extensive nor significant Medial calcification is common especially in those accustomed to manual labor Apparently because of its relation to physical movement, calcification is always more common in the vessels of the lower than of the upper extremity *But in neither site does it often impair the function of the vessel by leading to occlusion* In contrast medial calcification is uncommon in the coronaries, occurring in about 10 per cent of adults Thus the state of central arteries notably the coronaries cannot be estimated by radial palpation

The quality estimated in the sensation of radial thickening is obscure In senescence it is not an intimal change it may express medial calcification and fibrosis In hypertension it indicates the tonic contraction of the vessel *for muscular arteries like muscular arterioles are constricted by this disease* Continued arterial work leads to hypertrophy and some fibrosis these also may be apparent to palpation Clearly radial thickening does not deserve the emphasis which some clinicians have placed on it

The disease patterns of other muscular arteries such as the brachial and femoral are much the same as those in the radial To the brachial artery the common *site of estimations of arterial pressure,* we *have referred*

of the lesion suggests infection but rather because it is in appearance inflammatory Either arteriolar change leads to occlusion and exudate forms around the necrotic areas extending out into tissues whose blood supply is still intact and choking them off as flames pass from one crowded house to another

In essence the difference between essential and malignant hypertension is the difference between sclerosis and necrosis between aging and death A necrotizing vascular change occurs in normal people in areas of inflammation and in the uterus during involution By analogy with uterine arterioles the vascular lesions of malignant hypertension may be viewed as a sort of intensely accelerated regression while by analogy with arterioles in areas of inflammation the participation of toxic products of tissue decomposition may be supposed. In the latter connection there is good evidence that vascular lesions similar to those of malignant hypertension may be initiated by the injection of tissue extracts particularly extracts of renal tissue Thus malignant hypertension may represent the introduction into the pattern of hypertension of an obscure angiotoxic factor Since these changes are most common and severe in the kidneys where they cause widespread injury attention has concentrated on the association of this type of injury with renal failure Under Fahr the concept has crystallized into that of malignant nephrosclerosis a term which presupposes the coexistence of necrotizing arteriolitis and renal failure But most observers agree that its precise histologic delimitation is difficult Especially should it be pointed out that a lesion which must inevitably cause severe renal injury will at the end of its course often be associated with renal failure This however is not evidence that renal failure is cause of the arteriolar lesion Nevertheless whatever its origin the lesion soon reduces the perfusion of vital tissues and impairs their function and thus underlies the rapid and destructive course of a disease in which it is as if the arterioles were trees in a forest on fire In such cases the phase of vascular adjustment is necessarily brief

normal people as part of the regression of lymphoid tissue, but in the kidney, the change is almost a characteristic of hypertension

The changes thus far considered although they go on ultimately to obliteration of the vessels and death of tissues beyond progress slowly However other patterns may appear whose character differs sharply from the accelerated arteriolar senescence of most hypertensives These changes are therefore almost pathognomonic of hy

TABLE 6 —RATIOS OF WALL TO LUMEN IN ARTERIOLES OF NORMOTENSIVES AND HYPERTENSIVES

SITE EXAMINED	AUTHOR	NORMAL	HYPERTENSIVE GROUP 2	3	4	Whole Group
Myocardium	Odel	0 48				0 51
Pancreas	Morlock	0 41	0 62	0 77	0 84	
Liver	Morlock	0 43	0 59	0 77	0 9	
Gastrointestinal	Morlock	0 47	0 64	0 86	0 88	
Spleen	Morlock	0 75	0 81	0 92	0 96	
Kidney	Cain	0 52			1 4	0 9
Brain	Rosenberg	0 285			0 58	
Muscle	Kernohan *et al*	0 5			0 9	
	Wagener and Keith	0 5	0 76	0 76	0 83	
	Heyer and Keeton	0 5			0 96	
	Foa Foa and Peet	0 6				1 8
	Moritz and Oldt	0 53				0 74
Skin	Farber *et al*	0 47	0 65	0 60	0 65	0 72

Groupings 2 3 a d 4 ba ed on cl ss fication of Ke th and Wagener (p 7)

pertension and especially of malignant hypertension Usually at younger ages and always with a rapid downward course the arteriolar changes become correspondingly more severe and diffuse The smallest arteries exhibit widespread and intense occlusive intimal endothelial proliferation The arterioles instead of passing slowly through hypertrophy and sclerosis with intimal hyalinization develop sweeping changes in structure In a less intense phase the whole vessel assumes the character of fibrinoid necrosis, in which the cells die and are infiltrated with fibrin like material in a more severe phase the cells die and become infiltrated with exudate containing red and white cells a process called necrotizing arteriolitis The suffix itis in this case is given not because the character

of the lesion suggests infection but rather because it is in appearance inflammatory Either arteriolar change leads to occlusion and exudate forms around the necrotic areas extending out into tissues whose blood supply is still intact and choking them off as flames pass from one crowded house to another

In essence the difference between essential and malignant hypertension is the difference between sclerosis and necrosis between aging and death A necrotizing vascular change occurs in normal people in areas of inflammation and in the uterus during involution By analogy with uterine arterioles the vascular lesions of malignant hypertension may be viewed as a sort of intensely accelerated regression while by analogy with arterioles in areas of inflammation the participation of toxic products of tissue decomposition may be supposed In this latter connection there is good evidence that vascular lesions similar to those of malignant hypertension may be initiated by the injection of tissue extracts particularly extracts of renal tissue Thus malignant hypertension may represent the introduction into the pattern of hypertension of an obscure angiotoxic factor Since these changes are most common and severe in the kidneys where they cause widespread injury attention has concentrated on the association of this type of injury with renal failure Under Fahr the concept has crystallized into that of malignant nephrosclerosis a term which presupposes the coexistence of necrotizing arteriolitis and renal failure But most observers agree that its precise histologic delimitation is difficult. Especially should it be pointed out that a lesion which must inevitably cause severe renal injury will at the end of its course often be associated with renal failure This however is not evidence that renal failure is cause of the arteriolar lesion Nevertheless whatever its origin the lesion soon reduces the perfusion of vital tissues and impairs their function and thus underlies the rapid and destructive course of a disease in which it is as if the arterioles were trees in a forest on fire In such cases the phase of vascular adjustment is necessarily brief

Thus far we have dealt largely with the histologic character of the arteriolar changes visualizing them in the dimension of a histologic section, whereas in patients they are three dimensional Viewed thus, at the outset of hypertension, depending on the patient s age the arterioles may already be the seat of minor degrees of regression Here and there are areas of fibrosis, permitting the wall to dilate and the vessel to stretch and become tortuous while in some areas there are irregularly disposed plaques of intimal hyaline These senescent changes in normotensives occur in order of decreasing incidence in the spleen, pancreas adrenals, gastrointestinal tract, brain, muscle liver and in about 6 per cent of cases, in the kidneys Because they are changes of senescence, they increase with age but ordinarily do not threaten life When to this process hypertension is added, the arterioles become constricted and the persistent constriction leads to hypertrophy Hypertrophy in turn leads to fibrosis while intimal changes go on and begin to close the lumen Thus the arteriole at first straightens and thickens later shows irregularity of outline and perhaps aneurysmal dilatations while the lumen is encroached on and finally closed This sequence of change the result of hypertension is most common in the spleen kidneys and adrenals and less common in the pancreas gastrointestinal tract skeletal muscle and brain But in considering the incidence of such lesions in hypertension it is important to note that most observations have been made in patients who have succumbed to the disease so that the estimates do not apply numerically to living hypertensives and especially they do not apply to patients in the stage of adjustment to the disease However it is during this period that these changes begin and that upon them form the sequelae of local and systemic injury Further the severity of hypertensive arteriolar change at death reverses the rule of normotensives and is less severe as age increases Apparently the acute reactivity of the vessels decreases with advancing age although the tendency to sclerotic and hyaline

changes may be increased Hypertension is therefore more often severe and malignant in younger people

BIBLIOGRAPHY

ALLBUTT C. Diseases of the Arteries Including Angina Pectoris (London Macmillan & Co Ltd 1915)

ANDRUS F C The relationship of age and hypertension to the structure of the small arteries and arterioles in skeletal muscle Am. J Path. 12 635 1936

CAIN E F Malignant hypertension The histologic changes in the kidneys Arch. Int. Med 53 832 1934

COHN A E Cardiovascular system and blood in Cowdry E. V (ed.) Problems of Aging (2d ed. Baltimore Williams & Wilkins Company 1942)

COWDRY E V The structure and physiology of blood vessels in Cowdry E V (ed) Arteriosclerosis (New York The Macmillan Company 1933)

Editorial Advances in muscle physiology J A. M. A. 121 347 1944

FAHR G The heart in hypertension J A. M. A. 105 1396 1935

FARBER E. M. HINES E. A., JR. MONTGOMERY H AND CRAIG, W M Arterioles of the skin in essential hypertension J Invest. Dermat. 9 285 1947

FOA, P P FOA N L, AND PEET M. M. Arteriolar lesions in hypertension A study of 350 consecutive cases treated surgically An estimation of the prognostic value of muscle biopsy J Clin Investigation 22 727 1943

GREEN H. D Circulation Physical principles in Glasser O (ed) Medical Physics (Chicago Year Book Publishers Inc. 1944)

HEYER H. E., AND KEETON R. W Arteriolar changes of skeletal muscle in patients with hypertension of varied origin Am. J Clin. Path. 11 818 1941

KIMMELSTIEL, P AND WILSON C. L Benign and malignant hypertension and nephrosclerosis A clinical and pathological study Am. J Path. 12 45 1936

LANDOWNE, M. AND KATZ, L. N Heart Work and failure in Glasser O (ed) Medical Physics (Chicago Year Book Publishers Inc. 1944)

MORITZ, A. R. AND OLDT M. R. Arteriolar sclerosis in hypertensive and non hypertensive individuals Am. J Path. 13 679 1937

MORLOCK, C. G Arterioles of the pancreas liver gastro-intestinal tract and spleen in hypertension, Arch. Int. Med 63 100 1939

MURPHY F D AND GRILL, J So-called malignant hypertension A clinical and morphologic study Arch. Int. Med 46 75 1930

ODEL, H. M. Structural changes in arterioles of the myocardium in diffuse arteriolar disease with hypertension group 4 Arch. Int Med 66 5/9 1940

PAGE I H Arteriosclerosis and lipid metabolism in Cattell J (ed.) Biological Symposia Vol XI Aging and Degenerative Diseases (Lancaster Pa. Jaques Cattell Press 1945)

PRINZMETAL, M SIMKIN B BERGMAN H C. AND KRUGER H E. Studies on the coronary circulation II Am. Heart J 33 420, 1947

ROSENBERG E. F The brain in malignant hypertension Arch Int. Med 65 545 1940

SAPPINGTON S W AND COOK H S Radial artery changes in comparison with those of coronary and other arteries Am J M. Sc. 192 832 1936

SCOTT R D AND SEECOFF D P Arteriolar lesions of skeletal muscle in hypertension, Tr A. Am. Physicians 48 283 1933

WAGENER H P AND KEITH N M Diffuse arteriolar disease with hypertension and the associated retinal lesions Medicine 18 317 1939

WEARN J T Morphological and functional alterations of the coronary circulation Harvey Lect 35 243 1939 40
WEISS S AND ELLIS L B The quantitative aspects and dynamics of the circulatory mechanism in arterial hypertension Am Heart J 5 449 1929
WIGGERS C J Physiology of the coronary circulation in Levy A L (ed) Diseases of the Coronary Arteries and Cardiac Pain (New York The Macmillan Company 1936)
——— Physiology in Health and Disease (3d ed Philadelphia Lea & Febiger 1939)
——— Basic hemodynamic principles essential to interpretation of cardiovascular disorders Bull New York Acad Med 18 3 1942
WOLKOFF K Ueber die Atherosklerose der Coronararterien des Herzens Beitr z path Anat u z allg Path 82 555 1929

9 Clinical Considerations in Early Hypertension

I THORACIC ZONE

HEART CORONARY ARTERIES and aorta give rise to so many symptoms and signs in common that they form a unit for purposes of examination and treatment

By definition symptoms of organic cardioaortic disorder cannot be due to hypertension in the phase of adaptation But serious sometimes fatal disorders of the coronary arteries may appear early in the course of hypertension and are more probably incidental than sequential Thus coronary thrombosis and myocardial infarction may occur at any age and in the young are more to be associated with overnutrition or defective cholesterol metabolism than with hypertensive vascular disease But once the diagnosis of essential hypertension is established clinical distinction between the arterial disease it causes and that which may occur independently is difficult.

CARDIAC NEUROSIS

The early symptoms of hypertension have the general pattern of diffused anxiety and are conditioned more by the patient's personality than by the nature or severity of his disease Symptoms are often most severe in patients whose functional and structural disturbance of circulation is least important One form in which they appear is

cardiac neurosis The term is not well chosen It seems to have been more the expedient choice of the busy practitioner than the deliber ate conclusion of the psychiatrist As commonly used it has two or more meanings In one specific sense it refers to a somatic anxiety neurosis whose psychic pattern is not necessarily consciously associat ed with the heart but whose symptoms are those of cardiac disorder without hypertension These group themselves in the pattern of neurocirculatory asthenia or effort syndrome In this meaning the term has no more than incidental association with hypertension Studies by Friedman and by Cohen and others with Stanley Cobb have now greatly clarified its nature as a basic constitutional defect which becomes manifest under stress In quite another sense but with similar physiologic change the term cardiac neurosis applies to anxiety, present consciously or unconsciously in a patient who has hypertension or other organic heart disease and which has come to be centered on the heart It is in this sense that the term applies to our discussion

As we have seen many hypertensive patients have a full load of doubt fear and anxiety which they are only too willing to rational ize at whatever cost to themselves, around the heart In varying degree this is the case with most people hypertensive or not for the heart is full of emotional meaning Any threat to it is profound and altogether unacceptable People who will receive with perfect com posure the information that all is not well with the liver kidneys or stomach can be shaken to the core by a hint that the heart is en dangered A neurosis can thus be initiated which is similar in kind although not usually in degree or depth to that of neurocirculatory asthenia

Cardiac neurosis may be precipitated by the mis statement under statement over statement or over dubious statement of the exam ining physician He may misstate by wrongly suggesting the pres ence of heart disease in word or deed e g unexplained and unindi cated administration of digitalis or other cardiac drug He may over

emphasize the effects of hypertension on the heart perhaps by a too solicitous demand for further study or by a disproportionate interest in the heart during examination. In understatement the question of heart disease may be dismissed without what seems to be adequate consideration Possibly surest of all the neurosis may arise in doubt created by the physician who maintains and reveals an air of honest indecision This may prompt him to say I do not *think* you have heart disease It is safe to assume that every patient with hypertension is susceptible to this neurosis A circumspect manner and ordered routine of examination are the means of avoiding the pitfalls we have mentioned After the preliminary study is complete when data are at hand which satisfy the physician that his estimate is correct, when by the contact of history taking and examination the patient feels bound to the physician and is convinced of his interest and ability the time has come for the physician to tell him, There is nothing the matter with your heart In the absence of pre-existing cardiac neurosis the statement will be received in good faith

There remain to be prevented those cardiac neuroses which may develop outside the physician s office perhaps imitatively from contact with a case of heart disease in the home or immediate social circle perhaps from symptoms which direct attention to the heart during a prolonged and profound emotional disturbance These neuroses may be prevented by the patient s trust in the prior advice and examination Indeed the physician who hears that something has happened to his patient which might precipitate such a neurosis is justified in suggesting without reference to the event an early visit during which he listens to the patient s story encourages and reassures him

The difficulty in treatment of established cases varies with the intensity of the underlying anxiety and the time during which the patient has comforted himself with the belief that he is the victim of heart disease When the neurosis is intense psychiatric assistance may be necessary although as Weiss points out generally it is th

attending physician who must assume the responsibility and care of such patients In this, the attitude of the physician is as important as that of the patient A few patients will be content after a thorough review, with explanation and reassurance But most of them will still have to gain insight into the emotional origin of their symptoms

Two factors contribute to persistence of symptoms one is failure of *emotional acceptance, the other, poor physical condition the* result of having lived as one in cardiac failure Because of physical weakness and possibly of malnutrition due to ill advised and faddish diet effort may cause him to be short of breath or to tire easily Doubt returns and the syndrome persists Complete functional restoration of such a patient must be gradual if he is to avoid this difficulty and it must be coupled with renewed assurance and explanation His first tasks will be easy and the encouragement direct In setting out on this pattern Weiss suggests two useful sentences One is This much we know you can do and you must do it regardless of how you feel The other I will accept the responsibility for anything that happens to you does not carry much conviction to the legalistic *mind but is often persuasive*

Drugs have little place in the treatment The cardiac drugs such as digitalis and aminophylline which the patient may have been given are withdrawn once the diagnosis is made and accepted Any drug used should be clearly understood by the patient to be a palli*ative crutch which has nothing directly to do with his heart* Mild sedatives with prolonged action such as phenobarbital and hypertensive mixture (p 103) will be useful as occasionally will thiocyanate or a mixture of bromide and thiocyanate The general reorientation of regime and outlook advised for hypertensives may be *sufficient to alleviate symptoms In many moderate smoking will do* more to relieve tension than to provoke symptoms In some whose neurosis focused on the heart because of arrhythmias related to the use of coffee or tobacco limitations in their use will be prescribed

with the explanation that, because of their direction of emotion to the heart the heart is temporarily sensiti ed to their action Limita tion of consumption of coffee is easily endured but some may find restrictions on the use of tobacco more difficult than its interdiction Should this seem the case the physician should suggest a substitute means of oral gratification such as eating candy or chewing gum

EXAMINATION

The purpose of the examination is to discover the extent to which the heart and great vessels depart from the pattern of com plete adaptation in the direction of failure This information is ob- tained chiefly by measuring the size and estimating the quality of these structures The examination follows the usual outline anam nesis (with guarded and dexterous inquiry as to familial heart dis ease) and physical and laboratory examination

Physi al examination—Inspection and palpation together serve the examiner well A reliable index to cardiac hypertrophy is the position of the apex beat Its absence even when the patient leans forward does not exclude hypertrophy in persons with thick obese or emphysematous chests Much of the early enlargement of the left ventricle occurs laterally and posteriorly in the chest, so that the apex is rotated nearer the chest wall The position of the apex beat need not be shifted laterally at first The borders of cardiac dulness notoriously difficult to establish may seem and in fact may be of normal contour Of course the contour is often unconsciously dis placed leftward and upward by the examiner once the blood pres sure is known

The character of the apex beat has much to do with its interpre tation In hypertensives in the early phase of adjustment it should be forceful not only because the altered position of the heart brings the apex closer to the chest so that it is superficial but also because there is added quality of thrust and heave which testifies to increased myocardial effort. In moderate hypertrophy the beat moves down

ward to the sixth intercostal space its position relative to the mid clavicular line need not change With further progress there develops evident lateral displacement of the beat outward and downward

As with cardiac borders, percussion of para and retromanubrial dulness is not usually informative regarding the early response of the aorta and elastic vessels to hypertension Inspection and palpation of the suprasternal notch may establish the presence of undue aortic pulsation, the lengthening of the aorta indicates decreased elasticity A similar pulse due to excessive aortic filling rather than to diminished response, may be seen in hyperthyroidism In some patients, especially women past middle age, the innominate artery may present as a rounded pulsatile swelling beneath the roots of the sternocleidomastoid muscle This appearance which may extend to the right carotid is sometimes mistaken for aneurysm, which it is not Rather it is a local expression of elastic tissue regression

Auscultation —The first sound is composed of vibrations set up by ventricular contraction in the heart (in auriculoventricular valves chordae tendineae and ventricular wall) and possibly by the impact of systolic thrust against the chest Its intensity is a *guide to* the tension developed in the muscle early in systole and to the rate with which this tension arises In hypertension the first sound is large because of increased *absolute* tension in mitral stenosis it is also loud but here it would seem to be due to a rapid *rate* of *increase in tension The loud sound of mitral stenosis* has therefore the short character of a slap that of hypertension is prolonged and low pitched

Among the modifications of apical sound which may be heard in hypertensives one of great significance is protodiastolic gallop This is best heard in the left lateral decubitus position An indistinguishable third heart sound is heard at times in healthy youths or may appear in hyperthyroidism This is believed to reflect the reaction of the ventricle to *filling before auricular contraction* It may therefore appear during auricular fibrillation In hyperthyroid

ism, filling is excessive but the myocardium is seldom greatly injured in the failing hypertensive filling may be normal but the myocardium is weakened. If the heart rate is rapid, 100 per minute or more this third sound may all but superimpose on the normal auricular sound, so that the sum of the two neither being easily audible at slower rates appears as a low pitched sound in a brief diastole It is this summation of sound which is believed to cause the most common form of gallop rhythm

When the rate is slow the protodiastolic sound alone may be audible and this faintly so that it may be difficult to place it in the cycle Its timing may be established by the examiner s fixing his attention alternately for several beats on the first and second sounds separately instead of listening as is customary to the two sounds as they succeed each other In practice the onset of gallop rhythm due to a protodiastolic sound in a patient suspected of having myocardial disease confirms the suspicion. It has been called the "cry of a heart for help" It is especially useful because its presence may be determined with no more complex instrument than the stethoscope

Of the sounds at the base of the heart, a loud aortic second sound which contrasts with the pulmonic second sound is an expression of increased systemic diastolic tension The vibration which gives rise to it may be palpably transmitted as a diastolic shock when this shock is obvious the increased intensity of vibration may be presumed to indicate a decrease in aortic elasticity As the aorta dilates into a broad chamber eddies appear in the stream of blood which give rise to a systolic murmur Such murmurs may occur for other obscure reasons so that the diagnosis of aortic dilatation from a systolic murmur alone is altogether unreliable As adjustment is lost and the left ventricle begins to fail, congestion increases in the lungs and the pulmonic second sound grows in intensity A change in the relative loudness of the sounds suggests the imminence of congestive failure their relationship noted at the first observation should be recorded for future reference

Pulsus alternans or a weakening of every other pulse beat is best observed during the auscultatory measurement of arterial pressure Near the upper level of systolic pressure the feebler alternate sounds may disappear Like gallop rhythm it is a common early sign of myocardial weakness It can be distinguished from regular premature contractions by an electrocardiogram

Diagnostic aids—At best evidence obtained from inspection palpation and auscultation is insufficient to establish the degree of cardioaortic change in the patient whose hypertension is in the early stage These methods become most useful only as adaptation is lost Further the examination leaves no permanent record from which the developing course may be traced Electrocardiographic and roentgen examinations compensate for much of this deficiency (pp 148 ff and 154 ff)

Treatment

Treatment of arterial and arteriolar disease in the stage of adaptation is prophylactic The results are therefore not easily assessed The aim is to remove or minimize factors seeming to contribute to the advance of arterial damage These are mechanical strain hyperlipemia and the unknown factor(s) which controls deposition and removal of lipid from arterial walls

The participation of *strain* is suggested by the predilection of atherosclerosis for points of branching and of reduced physical support Increased arterial pressure increases the strain to which these and other sites are exposed Therefore it may be assumed that a lowering of the average pressure will retard the development of atherosclerosis The lowering of pressure depends on the treatment of hypertension by means *reviewed elsewhere* (*psychotherapy* drugs diet and operations) The converse namely that the patient with unusually high pressure must rapidly and inevitably develop severe atherosclerosis is not true so that the physician need not be concerned when high pressure does not readily respond to therapy

Experimentally what seems to be genuine atherosclerosis can be produced in rabbits or chickens during the *hyperlipemia* which results from cholesterol feeding Clinically, disease in which hyper lipemia is common such as diabetes mellitus nephrosis myxedema and xanthomatosis predispose to atherosclerosis The bouts of hyperlipemia which may develop during attacks of obstructive jaundice may explain some of the inconstant association between cholelithiasis and atherosclerosis Clinical and experimental evi dence points to hyperlipemia as one factor in atherosclerosis The presence of hyperlipemia may be suggested by the milky character of serum withdrawn during fasting or measured by determination of serum cholesterol or lipid content The normal levels of serum cholesterol vary widely in any group although they tend to remain the same in any individual A concentration persistently greater than 250 mg per 100 cc is evidence in favor of hyperlipemia

Treatment of hyperlipemia varies with its underlying cause In many cases insulin alone to diabetics in ketosis will rapidly reduce the plasma lipid content to normal levels subsequent dietary control supplemented when necessary with insulin will prevent the return of the hyperlipemia Although this control may be achieved by diets rich in fat and low in caloric content, it is more easily accomplished by low caloric diets rich in carbohydrate and protein and poor in fat Unfortunately there is no evidence that such diets retard the development of arteriosclero is except pos sibly among diabetics

Dietary control is ineffective in the hyperlipemia of hypothy roidism The cardiovascular adrenal and systemic strains imposed by the use of thyroid extract in this disease provide a dilemma which must be solved in each individual case Two rules aid the solution (1) that the provision of thyroid extract be made slowly and in small doses as by weekly increments from ¼ to ½ gr (USP) (2) that the maintenance dose be adjusted to a point where the patient feels comfortable and has lost hyperlipemia but

where the basal metabolic rate remains somewhat under normal

Biliary disease may be treated surgically when the indication arises, palliatively, a simple preparation of choleretic bile salts may be given The dosage is adjusted to the tolerance and apparent need of the gastrointestinal tract at a level just below that at which diarrhea begins Nephrotic hyperlipemia hardly concerns this discussion since it is not often associated with hypertension The lipemia in such cases is not affected by diets low in fat or by the use of thyroid extract, but only by remission

Although control of hyperlipemia is desirable and may prevent or retard the onset of atherosclerosis, there is nothing to suggest that the normal plasma content of lipid is noxious or that atherosclerosis in normal people can be affected by variations in dietary fat Indeed the postabsorptive plasma lipid content of the Eskimos—a people who subsist largely on protein and fat—is not high Fat absorbed from the alimentary canal is rapidly deposited in tissue depots and during postabsorptive periods its release from these depots maintains the plasma lipid concentration Since the plasma lipid content is largely independent of the dietary fat one is not justified in eliminating ordinary amounts of fat from the diet in the hope of reducing lipemia and preventing atherosclerosis Nutrition and palatability are not easily preserved on fat free diets They should be restricted to occasions when they are of proved advantage

There remain unknown or imperfectly defined factors which determine the deposition and retention of lipid in the arterial walls and the formation of atherosclerotic scars One of these is found in the specificity which permits establishment of experimental cholesterol atherosclerosis in rabbits and not in normal dogs and rats although it can be produced in dogs fed thiouracil and cholesterol Another lies in the effects of certain substances which prevent the deposition of lipid in the arterial walls of rabbits Thus the administration of *thyroid extract to cholesterol fed rabbits prevents hyper*cholesteremia and atherosclerosis in normal although not in thy

roidectomized animals potassium iodide has a similar preventive effect. An organic preparation of iodine the di iodide of ricinoleic acid, inhibit, development of experimental atherosclerosis in rabbits although hyperlipemia is unchanged or increased A similar effect is attributed to potassium thiocyanate garlic oil lipocaic and with more hope than belief ethyl alcohol. Among all these the best es tablished is iodide Whether it might act similarly on the vessels in the absence of hyperlipemia in human beings is not known Time honored practice sanctions its use once sclerosis has developed this practice had its origin in the treatment of syphilis and was then transferred to other cardiovascular diseases Experience has not been sufficiently rewarding to maintain the tradition into modern days However although iodide may be ineffective in the treatment of established atherosclerosis its effects in rabbits clearly indicate that it might have value in the formative stage of the human disease The drug is not ordinarily harmful in pharmacopeial dosage, given in interrupted courses of about a month the annoying consequences of abnormal sensitivity may be avoided by a searching history and the use of preliminary small test doses Clinical trial of iodide is therefore justifiable But evidence for or against its routine use must come from the study of large groups of patients und r controlled conditions

Cardiac hypertrophy—Hypertrophy proceeds from overwork and marginally adequate blood supply capillary and arterial Its prevention can be approached from the aspect of work by reducing the demand on the heart or increasing the efficiency with which it functions Reduction of demand implies the control of hypertension by the general measures recommended elsewhere and by means of subcaloric diets the reduction of weight and over all metabolism The problem of increasing cardiac efficiency is not solved although Starr s studies of the circulation point the way Experimentally administration of digitalis retards *hypertrophy* and maintains the chemical constituents of the myocardium in the face of the load im

where the basal metabolic rate remains somewhat under normal

Biliary disease may be treated surgically when the indication arises, palliatively, a simple preparation of choleretic bile salts may be given The dosage is adjusted to the tolerance and apparent need of the gastrointestinal tract at a level just below that at which diarrhea begins Nephrotic hyperlipemia hardly concerns this discussion since it is not often associated with hypertension The lipemia in *such cases is not affected by diets low in fat or by the use of thyroid* extract, but only by remission

Although control of hyperlipemia is desirable and may prevent or retard the onset of atherosclerosis there is nothing to suggest that the normal plasma content of lipid is noxious or that atherosclerosis in normal people can be affected by variations in dietary fat Indeed the postabsorptive plasma lipid content of the Eskimos—a people who subsist largely on protein and fat—is not high Fat absorbed from the alimentary canal is rapidly deposited in tissue depots and during postabsorptive periods its release from these depots maintains the plasma lipid concentration Since the plasma *lipid content is largely independent of the dietary fat, one is not* justified in eliminating ordinary amounts of fat from the diet in the hope of reducing lipemia and preventing atherosclerosis Nutrition and palatability are not easily preserved on fat free diets They should be restricted to occasions when they are of proved advantage

There remain unknown or imperfectly defined factors which determine the deposition and retention of lipid in the arterial walls and the formation of atherosclerotic scars One of these is found in the specificity which permits establishment of experimental cholesterol atherosclerosis in rabbits and not in normal dogs and rats although it can be produced in dogs fed thiouracil and cholesterol Another lies in the effects of certain substances which prevent the deposition of lipid in the arterial walls of rabbits Thus the administration of thyroid extract to cholesterol fed rabbits prevents hyper*cholesteremia* and atherosclerosis in normal although not in thy

210/120 mm Hg Neither answer is the wise one In the first case the patient will compare this value with that of others he may know and often go on to correlate his symptoms and his blood pressure level As in all cases where men meddle with medical science for a special purpose having no previous acquaintance with it his *imagination found what it wanted in books* Thus Holmes in *Elsie Venner* The white lie is even more dangerous The patient whose attitude seems to demand it will almost certainly consult another physician a quack or a midway manometrist and be told the true level of his pressure The little confidence he may have developed will be blasted and a working therapeutic regime interrupted or destroyed

The proper answer is neither the truth nor the half truth but the whole truth The patient is told that his blood pressure is increased and that increased pressure is *one part not the most significant*, in the estimate of his condition He is told how blood pressure varies so that differences of a few or many millimeters— points in this discussion—in single determinations are not *interpretable* and that even the trend of pressure is significant only as other factors can be determined. A demonstration of the dissociation between symptoms and blood pressure may be necessary Thus in hot weather the patient may *feel* blood rushing to his head and believe his pressure increased when actually it is decreased On another occasion when he feels well the level may be higher than when he felt unwell *Such experiences* may interrupt the tendency to interpret symptoms in terms of blood pressure and to consider blood pressure as an index of illness Finally he must be convinced that the figures are only useful *in their interpretation* and once diagnosis is made have little intrinsic value to the physician and none to him Repeated determinations made without comment and the progress of confidence will make the patient content to leave the values with the physician There are only rare exceptions to this experience

posed by aortic regurgitation Eventually, criteria may be defined which will permit the selection of patients in whom digitalis or some other drug may have a similar effect But such do not yet exist and digitalization has been known to provoke angina when given hypertensive patients not in cardiac failure Routine use of digitalis in patients with uncomplicated hypertension is therefore contra indicated

From the aspect of the coronary circulation demonstrably ade quate at this stage of the disease but presumably slowly deteriorat ing little can be suggested that is definite Some physicians believe that some benefit is obtained from oral administration of a xanthine vasodilator such as aminophylline or a theobromine compound alone or in combination with a sedative such as phenobarbital or amytal* The evidence for such treatment does not go beyond the stage of clinical impression and the purine component when given orally in small doses has been semiofficially discredited Still pending further evaluation administration of purine compounds such as theobromine and sodium acetate (0 5 Gm 7½ gr four times daily) may be helpful in patients whose coronary circulation is in some way or at some times inadequate Enteric coating of such tablets leads to irregular and sometimes deficient absorption

The disclosure—The argument that the discovery of hyperten sion unnecessarily terrifies the patient is invalid The discovery may terrify or unsettle the physician who is uncertain in his own mind and he may transmit his doubt to the patient The patient s doubts thus reinforced from the very source of expected direction and con trol may build up into terror

Part of the embarrassment the sphygmomanometer creates arises from the layman s childlike faith in it or in almost any device of biologic measurement and from the question he will ask What is my blood pressure? Three sorts of answer may be made One is direct giving the exact figures Another is the white lie in which the value chosen is perhaps 150/90 when the observation was

light and shade is so slight that it is necessary to inspect the contours one by one using shutters although a preliminary general view of the cardiac silhouette should be obtained in each position

The initial view is posteroanterior with the patient facing the screen Here the right border from the diaphragm upward consists of right auricle and ascending aorta which form two arches slightly converse laterally The left border above reveals the curved knob of the aortic arch below this is the flattened slightly concave or convex surface of the pulmonary artery and pulmonary conus interrupted at the point where the convexity of the left ventricle begins This point of separation may be found by inspecting the character of pulsation which in the left ventricle is directed medially and in the right upward The point on the left border of adjacent opposite pulsation marks the upper end of the interventricular septum (see the New York Heart Association s *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*)

The patient is then observed in the right anterior oblique position in which the right shoulder is pointed to the edge of the screen Here the base of the shadow is formed by the vena cava right auricle and ventricle the anterior curve consists of right ventricle and conus below and ascending aorta above the posterior border is formed by the left auricle above and the right auricle and inferior vena cava below In the third position the left anterior oblique the base of the outline is formed by the right ventricle and the anterior curve by the right ventricle right auricular appendix and ascending aorta The posterior outline is formed by the left ventricle below and left auricle above a small indentation separating the two This outline should be separated from the vertebrae by a translucent space All three positions—posteroanterior right anterior oblique and left anterior oblique—may be necessary to satisfactory demonstration of the course and size of the aorta

The character of the general posteroanterior contour (first position) differs with body build In persons with high diaphragms or

II CARDIOAORTIC ROENTGENOLOGY

This topic can be considered only in outline It is reviewed because its results will serve the physician if their significance is fully appreciated These examinations are best conducted and interpreted by a specialist

The conventional radiologic methods used in study of the thoracic zone are fluoroscopy teleradiography and orthodiagraphy

Fluoroscopy permits the examiner to study many regions of the heart in some detail but leaves no permanent record Teleradiography of this region is done by making a film at a standard distance of 2 m (usually 6 ft in practice) from the x ray tube The patient s chest is against the film to obtain a posteroanterior projection The gap between patient and tube is chosen to limit to about 10 per cent the magnification of the cardiac shadow by the scattering divergent rays which leave the tube Orthodiagraphy, in which fluoroscopy is made quantitative, utilizes only the central rays, focusing them on the lateral borders and permitting the examiner to trace the outline of the heart on a screen

FLUOROSCOPY

Fluoroscopy is a most valuable procedure It does not require the special apparatus and technic of orthodiagraphy, it does allow the contours to be visualized in more than one position Even more than wide experience adequate dark adaptation of the eyes is the key to the method Fluoroscopy is not a procedure to be done on short notice or when time is pressing The purposes of physician and patient are best achieved by making appointments for the examination of a group and setting aside uninterrupted time for this purpose The examiner s eyes also enter into the method if the near point of accommodation is longer than the 8–10 cm distance necessary for the technic If such is the case a clear focus can be obtained by the use of lenses fitted for the purpose Fluoroscopic contrast of

light and shade is so slight that it is necessary to inspect the contours one by one using shutters although a preliminary general view of the cardiac silhouette should be obtained in each position

The initial view is posteroanterior with the patient facing the screen. Here the right border from the diaphragm upward consists of right auricle and ascending aorta which form two arches slightly converse laterally The left border above reveals the curved knob of the aortic arch below this is the flattened slightly concave or convex surface of the pulmonary artery and pulmonary conus interrupted at the point where the convexity of the left ventricle begins This point of separation may be found by inspecting the character of pulsation which in the left ventricle is directed medially and in the right upward. The point on the left border of adjacent opposite pulsation marks the upper end of the interventricular septum (see the New York Heart Association s *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*)

The patient is then observed in the right anterior oblique position in which the right shoulder is pointed to the edge of the screen Here the base of the shadow is formed by the vena cava right auricle and ventricle the anterior curve consists of right ventricle and conus below and ascending aorta above the posterior border is formed by the left auricle above and the right auricle and inferior vena cava below In the third position the left anterior oblique the base of the outline is formed by the right ventricle and the anterior curve by the right ventricle right auricular appendix and ascending aorta The posterior outline is formed by the left ventricle below and left auricle above a small indentation separating the two This outline should be separated from the vertebrae by a translucent space All three positions—posteroanterior right anterior oblique and left anterior oblique—may be necessary to satisfactory demonstration of the course and size of the aorta

The character of the general posteroanterior contour (first position) differs with body build In persons with high diaphragms or

of hypersthenic habitus, the outline is broad and horizontal, the left ventricle is clearly seen and the area of pulmonary artery and conus is concave, the apex is displaced laterally and is often hidden behind the diaphragm. The opposite pattern, that of a long and narrow heart, occurs in those who are thin and tall. In those of definite asthenic habitus the shadow is pear shaped and oblique in those of intermediate build.

Hypertensive hypertrophy affects the two fluoroscopically distinguishable parts of the ventricle in successive phases. The first area seen to be increased in mass is known as the "outflow tract," possibly because it is here that the fibers are more severely stretched by diastolic tension. This tract extends from apex to aortic valve. *Its enlargement is therefore associated with rounding of the left* ventricular curve which increases the distance between the point of adjacent opposite pulsations and the apex. The apex becomes *rounded* and *projects to the left* and down, so that it often appears below the dome of the diaphragm and behind shadows of colonic or gastric gas. Differentiation from a normal horizontal heart may be suggested by failure of the convex outline of the left ventricle to disappear in deep inspiration as it should in absence of hypertrophy. The second phase of left ventricular hypertrophy enlarges the "inflow tract," i.e. the zone from mitral valve to apex. This enlargement is best visualized in the left anterior oblique position. The shadow of the left ventricle in this portion is elongated and curved so that it begins to fill the space toward the vertebral bodies. Later this shadow bulges and overlaps the spine. Presence of this change establishes the diagnosis of hypertrophy.

The aorta is then inspected for elongation and dilatation. The ascending aorta is best seen in the left anterior and postero-anterior positions where, if elongated, it becomes convex anteriorly and the transverse portion is elevated to almost the level of the clavicles. If aortic fibrosis is marked, the abnormal density of its shadow separates it from the superior vena cava and the diameter may be

estimated Elongation causes the transverse knob to project into the left lung field and in it calcification may be seen Lengthening of the descending limb causes it to lie to the left of the vertebrae rather than in front of them The thoracic aorta is best visualized in the right anterior oblique position Its elongation curves it convexly to the left dilatation with fibrosis may take a spindle shape which may be visualized on the fluoroscopic screen even through the cardiac shadow

TELERADIOGRAPHY

Teleradiography permits the recording of changes in the cardio aortic zone This the physician can animate in his mind if he has also examined the patient under the fluoroscope Teleradiography alone serves as a point of departure for further films recording progress of the disease Much that is seen in the posteroanterior fluoroscopic view is visible in a posteroanterior teleroentgenogram but the finer delineation of left ventricular enlargement in terms of septal to apical distance anteriorly and of abnormal filling of the inflow tract posteriorly cannot be visualized. The left and right anterior oblique films however have considerable value in deter mining chamber enlargement and width of aorta Planimetric meas urement of the area of the shadow and calculation from this of cardiac volume is a refined technic although better practiced from an orthodiagram

Because measurement of maximal transverse cardiac diameter is simpler and not much less accurate it is more widely used The measurement is made as the sum of maximal projections of right and left heart borders from the middle line Comparison of this diameter with that of the thorax is a highly inexact method the width of the thorax does not vary exactly with the size of the patient and is altered by respiratory excursion and emphysema Ungerleider and Clark s comparison of observed transverse diame ter with standards of predicted normal based on height and weight

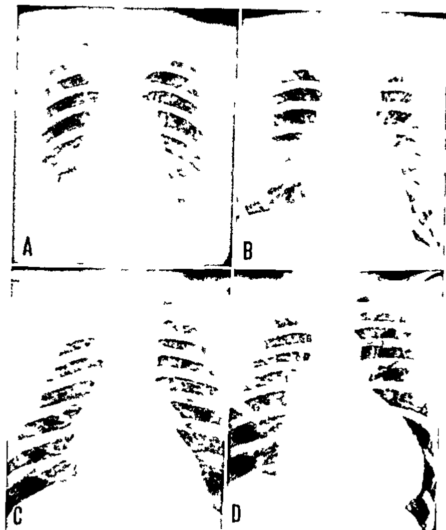


FIG 2—Teleroentgenograms showing *A* absence of cardiac enlargement *B* beginning enlargement of heart with widening of aorta *C* moderate enlargement *D* severe enlargement

is a valuable means of estimating hypertrophy (see chart p 385) Values which exceed the normal by 10 per cent suggest that hypertrophy has occurred and values of 15 per cent establish it

More elaborate and specialized technics which use x rays in the evaluation of cardiovascular disease are reserved for the study of diagnostic problems or for clinical investigation These include kymography angiocardiography and catheterization of the right auricle ventricle and pulmonary artery Kymography whether by roentgenogram or by the photomultiplier tube has its best application in detecting areas of infarction or aneurysm Angiocardiography applies in the detection of shunts congenital anomalies and in differentiation between aneurysm and tumor Catheterization applies in the study of congenital heart disease and in special clinical investigation None of these procedures applies directly to the problem of everyday essential hypertension except as in doubtful cases the angiocardiogram of the aorta may reveal coarctation of the aorta

Cardioradiography which uses the radiation of intravenously injected isotopic Na[4] has been described by Prinzmetal Preliminary studies indicate that this technic will have considerable value in the evaluation of many types of heart disease

BIBLIOGRAPHY

ANITSCHKOW N Experimental atherosclerosis in animals in Cowdry E V (ed) Arteriosclerosis (New York The Macmillan Company 1933)

Committees for the Standardization of Blood Pressure Readings of the American Heart Association and of the Cardiac Society of Great Britain and Ireland Standard method for taking and recording blood pressure readings J A. M. A. 113 294 1939

GOLDRING W AND CHASIS H Hypertension and Hypertensive Disease (New York The Commonwealth Fund 1944)

HIRSCH E F AND WEINHOUSE S Role of the lipids in atherosclerosis Physiol. Rev 23 185 1943

LEARY T Cholesterol lysis in atheroma Arch. Path 37 16 1944

Medical Department of the Equitable Life Assurance Society of the United States Roentgenology of the Heart (publication of the Picker X ray Corp)

PAGE, I H Some aspects of the nature of the chemical change occurring in atheromatosis Ann Int. Med 14 1741 1941

PRINZMETAL, M CORDAY E SPRITZLER R J AND BERGMAN H C Radiocardiography Am Heart J 36 406 1948 (abstr)

ROESLER H Clinical Roentgenology of the Cardiovascular System (2d ed Springfield Ill Charles C Thomas Publisher 1943)
SHERIDAN J T The transverse diameter of the frontal aortic arch silhouette A Life Insurance M Directors America 28 49 1941
STEELE J M Evidence for general distribution of peripheral resistance in coarctation of the aorta Report of three cases J Clin Investigation 20 473 1941
——— Comparison of simultaneous indirect (auscultatory) and direct (intra arterial) measurements of arterial pressure in man J Mt Sinai Hosp 8 1042 1942
STIEGLITZ E J Asymmetry of arterial tension in Abnormal Arterial Tension (New York National Medical Book Company Inc 1935)
The Criteria Committee of the New York Heart Association Nomenclature and Criteria for Diagnosis of Diseases of the Heart (New York New York Heart Association 1942)
UNGERLEIDER H E AND GUBNER R *Evaluation of heart size measurements* Am Heart J 24 459 1942

III THE ELECTROCARDIOGRAM

The electric currents of cardiac action as they appear in the electrocardiogram yield helpful almost essential information as to the structural and metabolic effects of hypertension on the heart That the method is not more widely and intelligently used is partly the result of misconceptions One of these is that the instrument is a tin and copper idol whose wavering runic lines can be scrutinized only by the oracular few Another is that its application is largely restricted to the diagnosis of acute and severe cardiac disease such as myocardial infarction The necessary changes in terminology and technic of recent years may also have discouraged its use But the advent of direct writing machines will expand use of this method

To avoid error assistance of a specialist must be sought especially for the accurate evaluation of minor changes He probably should supervise the making and interpretation of the record Still the patient s own physician is best able to fit this information into the pattern of his patient s illness thus he should have some appreciation of the patterns themselves

Movement of a wave of excitation over the auricles through the conducting muscular tissue to the inner ventricular surfaces and out into the ventricular myocardium is accompanied by changes

of electrical potential which the electrocardiograph records as galvanometric deflections The direction of the deflection varies up or down as the potential change is positive or negative

The distance through which a deflection extends from the isoelectric line of zero potential depends on the magnitude of potential difference itself the extent to which it is reinforced or neutralized by simultaneous potentials from some other site in the heart and the extent to which it is damped by tissue resistance The relative absence of damping by tissue substance accounts for the large deflections found in precordial leads Indeed these leads seem now ready not only to add to and perhaps replace but also to explain the patterns found in standard leads Hecht points out that being semidirect they are most like the leads taken directly from the surface of the heart and thus convey most adequately what is going on in it. But it is not our purpose to discuss the technic theory and practice of electrocardiography topics ably surveyed by Ashman and Hull Katz, Burch and Winsor Scherf and Boyd, Barnes and Hecht. Rather we are concerned with the changes in pattern found in hypertension and in hypertensive heart disease inasmuch as they indicate the presence of left ventricular hypertrophy and the advance of left ventricular strain

These pattern changes are seen in the standard limb leads and in precordial leads either CF (chest foot) or V (central terminal) Isolated observations are of much less value than records taken at routine intervals of months and years in detecting early changes in the pattern normal to the individual Even with isolated observations prognostic value of the electrocardiogram is emphasized by Gubner and Ungerleider They believe that it gives a more sensitive indication of hypertrophy than does the teleroentgenogram They found that the death rate for hypertensive patients whose electrocardiograms are even questionably abnormal is 2 7 times that for normotensive controls for patients with definite changes of moderate or severe degree the rate is 3 4–3 7 times normal

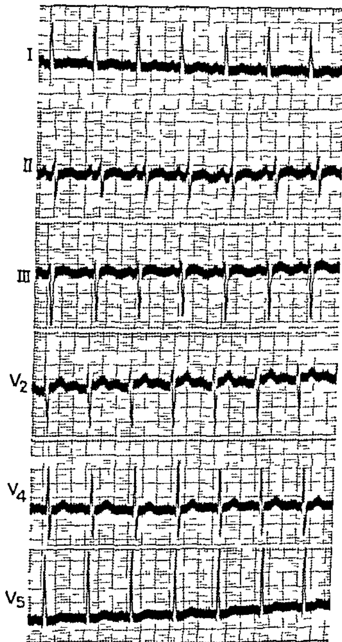


FIG 3A —Representative electrocardiogram from patient with moderately advanced hypertensive heart disease shows only the changes characteristic of moderate left axis deviation with some sinus tachycardia

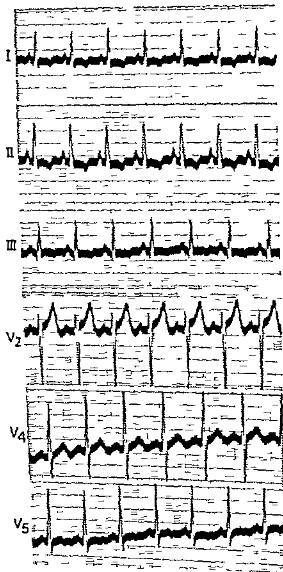


FIG. 3B—Electrocardiogram from pati nt w th severe rapidly advancing malignant hypertens on shows ev dence of left ventricular hypertrophy with myocardial change (note notching of R_3) and st a n (depression of $RS-T_1$ nd RS-T)

Left ventricular hypertrophy—The pattern change most characteristic of this condition is left axis deviation This consists in a deflection of mean electrical axis from its normal direction leftward and is due to the changes in position of the heart caused by hypertrophy First there is rotation and direction of the apex downward, followed by left lateral direction of the heart as a whole In other words the large heart is also usually horizontal The direction of the axis in health varies with body build, toward the right when the heart is normally vertical and toward the left when the diaphragm is high and the heart horizontal Transient left axis deviation can be caused by anything that elevates the diaphragm such as full forced expiration, pregnancy, ascites or other abdominal distention In some degree, it is normally present at rest in about 5 per cent of healthy young males

For most clinical purposes left axis deviation is considered present and presumably pathologic when the axis deviation index exceeds 20 This value is computed by measurement from the standard limb leads of the electrocardiogram as $(R_1 - S_1) - (R_3 - S_3)$ Such a change occurs in 60–80 per cent of patients with hypertension It never appears in some despite cardiac hypertrophy because hypertrophy has operated on a heart which in health was vertical

Its mechanism is best understood in terms of the changes in precordial leads and the reflection of the precordial potentials in standard leads These are in essence exaggerations of the mean normal toward the right side R waves become smaller and S waves deeper toward the left, Q waves become deeper R waves larger and S waves smaller As the pattern intensifies there follows depression and upward convexity of left precordial RS–T segments while the T waves become depressed diphasic or inverted When left axis deviation is not obvious in standard leads hypertrophy may reveal itself in the RS–T segments and T waves it is of course usually detectable from a study of precordial leads

It is customary in many circles to designate the RS–T and T wave changes caused by hypertrophy as evidences of left ventricular strain Some workers define strain as a pattern in which the RS–T segment is depressed 0 5 mm or more in lead I with or without corresponding elevation of this segment in lead III and with flattening inversion or other definite abnormality of T_1 While of some clinical advantage this diagnosis should be made with care especially in the presence of tachycardia or during administration of digitalis

Other electrocardiographic changes in hypertension—Terminally in malignant hypertension although not as often as in the uremia of chronic glomerulonephritis or chronic pyelonephritis the electrocardiogram reveals evidences of hyperpotassemia in peaked T waves or of a deficiency of ionizable calcium in the length of the Q–T interval Exceptionally uremic pericarditis leads to concurrent depressions of RS–T segments More frequently myocardial infarctions and coronary insufficiency cause electrocardiogram changes Sometimes smoking severe pain or anxiety or such a catastrophe as the dissection of an aortic aneurysm disturbs the pattern For the changes thus produced in the electrocardiogram and their explanation the reader is referred to standard texts

Finally much has been written on diagnosis by tests of latent coronary artery disease (disease which is perhaps causing some symptoms but which is not manifest in the electrocardiogram at rest) The tests are variously done by injection of pitressin* by submitting the patient to anoxemia or by exercise Results often are negative in patients who manifest coronary artery disease in other ways Some of the tests (pitressin* anoxia) may be dangerous and diagnostic accuracy is in any case not more than 50 per cent Clearly their inaccuracy is due to a failure to re-establish the full train of conditions which may have led to a heart attack Therefore they are not recommended except as specialized and investigational procedures

BIBLIOGRAPHY

ASHMAN R AND HULL E Essentials of Electrocardiography (2d ed New York The Macmillan Company 1941)

BARNES A R Electrocardiographic Patterns Their Diagnostic and Clinical Significance (Springfield Ill Charles C Thomas Publisher 1940)

BURCH G E AND WINSOR T A Primer of Electrocardiography (Philadelphia Lea & Febiger 1945)

DALEY R M GUBNER N S AND UNGERLEIDER H E Roentgenology of the Heart (Equitable Life Assurance Society of the United States publication of the Picker X ray Corp)

——— UNGERLEIDER H E AND GUBNER N S Prognosis in hypertension J A M A 121 313 1943

EVANS E MATHEWS M W AND WHITE P D The electrocardiogram in hypertension I Its description Am Heart J 30 140 1945

GUBNER R AND UNGERLEIDER H E Electrocardiographic criteria of left ventricular hypertrophy Arch Int Med 72 196 1943

HECHT H Basic Principles of Electrocardiography American Lecture Series (Springfield Ill Charles C Thomas Publisher in press)

HERRMANN G R Synopsis of Diseases of the Heart and Arteries (3d ed St Louis C V Mosby Company 1944)

KATZ L N Electrocardiography (Philadelphia Lea & Febiger 1941)

SCHERF D AND BOYD L J Cardiovascular Diseases (Philadelphia J B Lippincott Company 1947)

SECTION IV

10 Hypertensive Heart Disease

INABILITY OF THE vascular tree to adapt successfully to long standing severe essential hypertension is most often manifested by the onset of some form of hypertensive heart disease This complication overtakes some two thirds of those who suffer from hypertension and is the primary cause of death in most of these patients It constitutes the most common form of heart disease which occurs in people of mature years

Whatever form it takes hypertensive heart disease is due to inadequacy of coronary blood flow in proportion to myocardial need. When it appears as angina pectoris or as myocardial infarction due to coronary occlusion the lesion is arterial and the major defect a localizable decrease in the absolute rate of coronary blood flow In contrast in coronary insufficiency and congestive cardiac failure which are much the more common forms of hypertensive heart disease the major defect can be traced to the increased and untoward demands placed on the myocardium of the left ventricle by the presence of arterial hypertension

Both mechanisms the arterial and the myocardial combine in many patients and in varying degrees But even when the lesion is predominantly arterial hypertension adds a factor of myocardial strain and increased metabolic demand which must be harmful since its presence exaggerates the deleterious effects of ischemia It is therefore not surprising that the coronary arteriosclerosis which

commonly results in angina infarction coronary insufficiency or congestive failure in patients with hypertension is nearly always much less severe than the coronary arteriosclerosis which precipitates these ailments in normotensive people Hypertensive heart disease is a product of a vicious cycle in which arterial hypertension increases metabolic demand while it also favors the onset and progression of coronary arteriosclerosis This fact gives a clue to prognosis and treatment since it suggests that both will depend in large measure on the possibility of relief of myocardial strain by control of hypertension But in the discussion which follows, we are less concerned with the general measures for the control of hypertension (p 142) than with the immediacies of treatment of hypertensive heart disease

I ANGINA PECTORIS AND CORONARY INSUFFICIENCY

The syndrome of angina pectoris was described and named by Heberden (1710 1801) His classic description may be quoted in part After excluding as unimportant other types of chest pain he writes But there is a disorder of the breast marked with strong and peculiar symptoms considerable for the kind of danger belonging to it and not extremely rare which deserves to be mentioned at length They who are afflicted with it are seized while they are walking (more especially if it be up hill and soon after eating) with a painful and most disagreeable sensation in the breast which seems as if it would extinguish life if it were to increase or continue but the moment they stand still all this uneasiness vanishes In all other respects the patients are at the beginning of the disorder perfectly well and in particular have no shortness of breath from which it is totally different Heberden overlooked its mechanism Jenner (1749 1823) and Parry (1755 1822) believed that they had found its cause in disease of the

coronary arteries They refrained from publishing the discovery for 20 years lest the knowledge alarm John Hunter who during all this time had shown the symptoms Heberden described

A modern succinct and inclusive definition of the syndrome is given by T R. Harrison Angina pectoris is a common condition characterized by recurrent attacks of discomfort in or near the chest, commonly induced by conditions which impose an additional burden on the heart ordinarily dependent on disturbance of the oxidative processes in the myocardium and always at

TABLE —MOST IMPORTANT CLINICAL FEATURES IN DIAGNOSIS OF ANGINA PECTORIS (HARRISON)

I Features of Positive Value	II Features of Negative Value† (presence tending to exclude angina pectoris)
1 History of relation to effort	1 Pain limited to periapical axillary or abdominal regions
Sub ternal or precordial location	2 Duration of less than 1 minute
3 Duration 1–30 minutes	3 Lancinating or throbbing pain
4 Demonstration that nitroglycerin increases amount of effort required to induce pain	4 Aggravation by breathing, coughing swallowing sitting or standing

These clinical features are present 90 per cent more of p sent

†These features either re absent n angina pectoris o if present, re due o associated disorders

tended by the likelihood of sudden death To this we might add that Heberden observed that it was most common among males over age 50 in the proportion of 3 1 and that this ratio still obtains Among females predisposition is greatly increased by hypertension

The clinical diagnosis of angina pectoris is still difficult. As a result it is probably more frequently made than is warranted in that group who run to the physician with the least complaint—and who will take the most injury from the cardiac neurosis which thus may be thrust upon them—while it is likely to be overlooked among those who are less communicative in their descriptions Table 7 shows the important clinical features in diagnosis repro-

commonly results in angina, infarction coronary insufficiency or congestive failure in patients with hypertension is nearly always much less severe than the coronary arteriosclerosis which precipitates these ailments in normotensive people Hypertensive heart disease is a product of a vicious cycle in which arterial hypertension increases metabolic demand while it also favors the onset and progression of *coronary arteriosclerosis This fact gives a clue to prognosis* and treatment since it suggests that both will depend in large measure on the possibility of relief of myocardial strain by control of hypertension But in the discussion which follows we are less concerned with the general measures for the control of hypertension (p 142) than with the immediacies of treatment of hypertensive heart disease

I ANGINA PECTORIS AND CORONARY INSUFFICIENCY

The syndrome of angina pectoris was described and named by Heberden (1710 1801) His classic description may be quoted in part After excluding as unimportant other types of chest pain he writes But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it and not extremely rare which deserves to be mentioned at length They who are afflicted with it are seized while they are walking (more especially if it be up hill and soon after eating) with a painful and most disagreeable sensation in the breast which seems as if it would extinguish life if it were to increase or continue but the moment they stand still all this uneasiness vanishes In all other respects the patients are at the beginning of the disorder, perfectly well and in particular have no shortness of breath from which it is totally different Heberden overlooked its mechanism Jenner (1749 1823) and Parry (1755 1822) believed that they had found its cause in disease of the

ischemia that is the blood flow through the arteries may be deficient (*a*) because of systemic inadequacy of venous return and cardiac output or (*b*) locally because of vasoconstriction or of sclerotic obstruction (2) The disturbance may be myocardial the result of an excess of functional demand and/or the difficulty of meeting it imposed by hypertrophy or (3) it may be metabolic and arise from changes in the chemistry of blood (hypoglycemia anoxia or anemia) or tissue (loss of carboxylase in vitamin B_1 deficiency loss of creatine phosphate in myocardial failure) The manner of onset and character of the symptoms enable the physician to assess in part at least the culpability of each factor in the production of angina in the patient under study

AIDS TO DIAGNOSIS

Hypertensive patients who have angina commonly show electrocardiographic abnormalities during rest which signify as do their symptoms inadequacy of coronary perfusion These are marked deviations of S–T segment and T wave the evidences described earlier as strain and strain with fibrosis the presence of interventricular or auriculoventricular block The residue of old infarction in an abnormal Q_1 or Q_3 or inverted T_4 wave *may* be seen That such should be the case would be predicted from the almost uniform presence of old myocardial scars in anginal subjects A normal tracing does *not* exclude the diagnosis

Curiously just as angina is *infrequent* in *congestive* failure it is rare in patients with auricular *fibrillation* or flutter although it may appear *in* the intervals between attacks. An important characteristic of angina pectoris is that an attack spontaneous or voluntarily induced is rapidly cut short by the use of nitrites (p 170) Of th 25–50 per cent of patients with angina who do not show electrocardiographic abnormalities at rest more than half will develop them during exercise or during the other tests of latent coronary disease (p 159) Failure to reproduce the attack or to

duced from Harrison s tabulation That the significance of precordial or substernal pain can be overemphasized is shown by the 24 per cent of Proudfit and Ernstene s patients in whom pain was atypically distributed

The classic descriptions of *angina pectoris* and its aberrant patterns have, by their respective centerings of emphasis aided the growth of diagnostic misconceptions To these Harrison has also called attention Thus, he has noted that the pain may be mild and nonconstrictive, rather than severe and oppressive and that it may be neither substernal nor precordial in its principal locus and may at times wholly lack a substernal component Sometimes pain particularly that of status anginosus, in which anginal attacks succeed each other in rapid succession may be aggravated by recumbency In patients who *seem to be subject to hypoglycemia* Harrison has noted that the tendency to attacks may be relieved rather than increased by the ingestion of food Aggravation on recumbency and relief on taking food are not frequent in Barnes s experience or our own

On the other hand relief on standing erect suggests that the pain is more probably due to hiatus hernia than to coronary heart disease Pain which is increased by swallowing suggests the presence of esophageal spasm or cardiospasm (both of which may be relieved by nitrites) and pain related to movement of the head or arms may be due to cervical osteoarthritis

Mechanism

The pain of angina pectoris is believed to arise from irritation of myocardial nerve endings by accumulation of a *metabolic* product (or products) which can readily diffuse into the blood stream and which can be quickly altered in the presence of an adequate supply of oxygen The disturbance of oxidative process which gives rise to this hypothetical accumulation of P (for pain) substance may have one of several causes (1) It may result from

the flow of blood as well as increased cardiac work The physician need not fear but rather should rejoice in a reasonable decrease in arterial pressure obtained by a planned therapeutic regime A high arterial pressure is more of an obstacle than an aid to effective myocardial blood flow

Temporarily increased myocardial effort is the common immediate precipitating stimulus The patient is usually aware of the amount and type of activity he can tolerate He should be instructed above all to slow down in all activity and to keep well within the boundary of pain whatever the response to treatment Reduction of weight is clearly advisable among the obese since bodily movement increases cardiac work The subcaloric diet prescribed for this purpose has the additional advantage of reducing metabolic rate Some patients with angina have loose relaxed abdominal walls Kerr suggested that angina which occurs on effort and in the erect position in middle aged men may be related to orthostatic pooling of blood in the relaxed abdomen the resultant decrease in cardiac output provoking the attack Fitting of a suitable abdominal belt increased effort tolerance in such cases But this form of easily remediable angina is found all too rarely

In the coronary arteries vasoconstriction without arterial disease is rarely if ever a factor Rather the combined mechanisms of increased myocardial effort coronary vasoconstriction and obstruction by atherosclerosis underlie the process Although some means may be found to retard the progress of atherosclerosis there is no evidence that any are available which will remove it except possibly severe caloric restriction The principal aims of treatment must be the prevention or release of vasoconstriction and attempts at vasodilation which may speed formation of arterial collaterals

VASOMOTOR AND PSYCHOGENIC PRECIPITATION Vasoconstriction is commonly due to nervous stimulation In angina the modes of such stimulation whether psychic or reflex must be depressed The classic example of angina precipitated by psychic

cause abnormalities of the electrocardiogram by the exercise test may add to the difficulty of confirming a diagnosis based on the history and relief of pain by nitrite A falsely negative result of the test depends on failure to produce a precise deficit of myocardial perfusion Such failure may be evidence of the large number of factors emotional postural vascular and biochemical which enter into a typical attack

Many patients whose electrocardiograms are normal at rest show abnormalities during involuntary attacks In some the pattern of such an attack is localizable in the manner described later for recent coronary occlusion These patterns probably testify to the presence of old or to the imminence of new infarction of the myocardial areas to which they are referable

Treatment

The purposes of treatment are (1) the prevention of recurrent attacks with the hope of delaying or preventing a fatal issue in myocardial infarction or ventricular fibrillation (2) the relief of a developing or present attack and (3) the relief of intractable pain The first of these is the most important

Prevention —The methods used to prevent attacks depend on an evaluation of the degree to which ischemic myocardial and metabolic factors separately precipitate the seizure Predominance of myocardial disease is more commonly associated with congestive failure than with true angina the principles of its treatment are discussed later (p 187) To the extent that the myocardial defect is due to strain and increased mean arterial pressure its treatment is that of hypertension When the deficit of perfusion is due almost entirely to organic occlusion a great decrease in coronary blood flow may follow a relatively slight decrease in arterial pressure or with lesser degrees of obstruction occur in syncope However in hypertension the deficiency is conditioned by several factors notably vasoconstriction atherosclerosis increased tissue resistance to

the flow of blood as well as increased cardiac work. The physician need not fear but rather should rejoice in a reasonable decrease in arterial pressure obtained by a planned therapeutic regime A high arterial pressure is more of an obstacle than an aid to effective myocardial blood flow

Temporarily increased myocardial effort is the common im mediate precipitating stimulus The patient is usually aware of the amount and type of activity he can tolerate He should be instructed above all to slow down in all activity and to keep well within the boundary of pain whatever the response to treatment Reduction of weight is clearly advisable among the obese since bodily move- ment increases cardiac work. The subcaloric diet prescribed for this purpose has the additional advantage of reducing metabolic rate Some patients with angina have loose relaxed abdominal walls Kerr suggested that angina which occurs on effort and in the erect position in middle aged men may be related to orthostatic pooling of blood in the relaxed abdomen the resultant decrease in cardiac output provoking the attack Fitting of a suitable abdominal belt increased effort tolerance in such cases But this form of easily remediable angina is found all too rarely

In the coronary arteries vasoconstriction without arterial dis- ease is rarely if ever a factor Rather the combined mechanisms of increased myocardial effort coronary vasoconstriction and ob- struction by atherosclerosis underlie the process Although some means may be found to retard the progress of atherosclerosis there is no evidence that any are available which will remove it except possibly severe caloric restriction The principal aims of treatment must be the prevention or release of vasoconstriction and attempts at vasodilation which may speed formation of arterial collaterals

VASOMOTOR AND PSYCHOGENIC PRECIPITATION Vasocon striction is commonly due to nervous stimulation In angina the modes of such stimulation, whether psychic or reflex must be de pressed The classic example of angina precipitated by psychic

stimulation is that of John Hunter My life he said is in the hands of any rascal who wishes to worry and tease me Home wrote in his biographical note on Hunter It is a curious circumstance that the first attack of these (Hunter s) complaints was produced by an affection of the mind and every future return of any consequence arose from the same cause and although bodily exercise, or distention of the stomach brought on slighter affections it still required the mind to be affected to render them severe, and as his mind was irritated by trifles these produced the most violent effects of the disease His coachman being beyond his times or a servant not attending to his directions brought on the spasms while a real misfortune produced no effect At St George s Hospital he met with some things which irritated his mind and not being perfectly master of the circumstances he withheld his sentiments in which state of restraint he went into the next room and turning round to Dr Robertson he gave a deep groan, and dropt down dead

Hunter s case with predominant emotional precipitation of attacks and conceivably initiated by myocardial infarction is not typical for in only 10 per cent of Harrison s series was angina precipitated by emotion without exertion The mechanism of emotionally conditioned angina is probably multiple on one hand there may be direct vasoconstrictor impulses released by emotion on the other hand the increased blood pressure which emotion excites may cause the release of cerebral and sinoaortic reflexes which reduce the adequacy of myocardial perfusion or cause tachycardia and ectopic beats In either case a mental attitude which depresses the psychic provocations to angina is to be recommended as part of the general treatment of hypertension The relation between emotional upsets and anginal attacks should be brought to the patient s attention and he should be counseled on means of avoiding them Sedatives (phenobarbital 15–30 mg ¼–½ gr) three times a day and at bedtime may aid him When

life situation or personality difficulties seem to be major factors appropriate measures should be counseled.

VASOMOTOR REFLEX PRECIPITATION Reflex stimulation may arise in the skin (exposure to cold) or respiratory passages (breathing cold air walking against the wind) with disorders of function of the gastrointestinal tract or from pain in this or other regions Distention of the stomach or bowel by food or gas causes a sharp reduction in coronary flow Gilbert, Leroy and Fenn increased the sensitiveness of anginal patients to anoxia 20–40 per cent by feeding and abolished the effect of meals by atropine Any provocative activity should be avoided after meals when 60 minutes of rest in a chair or on a couch is advisable Bulky or gas forming meals carbonated drinks and air swallowing must be avoided. Constipation should be overcome by mild methods

Since smoking may induce anginal attacks or possibly *increase* susceptibility to them it is best avoided In *some* people smoking produces significant electrocardiographic *alterations* These changes added to those of the morbid process seem undesirable

Heberden found that wine and spirituous liquors and opium —the last then freely prescribed— afford considerable relief This relief may be prescribed with due regard to moderation as a glass of sherry an unchilled highball or an ounce of whiskey or in the evening as a hot toddy Studies have shown that alcohol does not directly affect angina as such apart from release from tension it may afford For *some* patients tincture of belladonna (5–15 minims 0 3–1 cc) taken 30 minutes before meals may be advantageous Reflex constriction from extracardiac pain may precipitate attacks or electrocardiographic abnormalities in patients not otherwise susceptible This seems especially true of biliary pain and discomfort Relief in each case depends on specific indication When biliary disease is present and operation is not contemplated administration of a simple preparation of bile salts is useful

VASODILATION After preventing constriction the next pro-

cedure is the provision of vasodilation One means to this end may be oral administration of xanthine compounds e g theobromine calcium salicylate (7½ gr, 0 5 Gm) or theophylline with ethylenediamine i e aminophylline (3 gr, 0 2 Gm), four times a day Both drugs are best tolerated when enterically coated however since the coating does not always dissolve coated tablets are sometimes ineffective Caffeine although a purine vasodilator should be avoided because of its cerebral action and its use as coffee should be limited. Alternatively papaverine (3 gr, 0 2 Gm) may be given orally three or four times a day It depresses ventricular excitability and may lessen one source of the patient s anxiety namely extrasystoles Its general usefulness is controversial Vasodilator tissue extracts have been tried but the effect is uncertain and the demands on physician and patient by daily injection are onerous Testosterone intramuscularly (as propionate 25 mg) three times weekly has been effective in some males However the expense may weigh heavily on those already greatly burdened It is not clear whether its action is one of vasodilation of hypogonadal relief or a direct action on the cardiac muscle as part of its claimed systemic tonic action

The attack—The physician having taken measures which prevent vasoconstriction and promote vasodilation must ordinarily leave actual treatment of the attacks to the patient The patient should know that he *must* rest during the attack He is given a vial of nitroglycerin tablets The more soluble hypodermic tablets are preferable the dose is 0 3–0 6 mg (1/200–1/100 gr) sometimes less and is selected by the patient s response when he dissolves the tablet under his tongue during an attack The tablet is used whenever an attack impends or occurs or when an unavoidable situation arises which the patient knows may provoke one A more rapid but somewhat less tasteful effect is secured by inhalation of amyl nitrite (0 12–0 18 cc) from a glass perle crushed in a handkerchief A timid patient is usually prevented from excessive dosage

of either nitrite by headache When due moderation rest and other measures do not prevent frequent attacks the doses of nitrite should be repeated as necessary as often as 20 times a day Since these drugs cause vasodilation and temporarily decrease venous return the patient should recline or sit when he takes them to avoid syncope and hypotension with its risk of acute coronary insufficiency

A group of nitrites which because of their slow gastrointestinal absorption have a sustained and delayed action are often used for their prophylactic value Erythrol tetranitrate (0 015–0 03 Gm ¼–½ gr) is taken by mouth its effect appears in about 15 minutes and lasts three hours Mannitol hexanitrate (0 06 Gm 1 gr) has a little slower action and lasts perhaps an hour longer The slowly acting nitrites have a limited usefulness They should not be administered unless it can be shown that they actually reduce the number of attacks of pain

Narcotics—like Heberden s opium in which the *non narcotic* vasodilator papaverine may have been a significant component—have no place in the treatment of an attack which subsides within 10 minutes Ordinarily a hypodermic injection cannot be given in much less time than it takes the attack to subside and when the severity and duration of an attack seem to require it the diagnosis should be questioned

Certain drugs should be avoided or used only for specific indications These are thyroid epinephrine ephedrine benzedrine* pituitrin* and usually thiocyanate Digitalis is used only in angina clearly associated with congestive failure for while it increases coronary blood flow in the dilated heart it may decrease flow in the undilated heart. This vasoconstrictor effect appears most often when the dosage is such as to cause other toxic side effects

A few patients remain whose pain is not prevented or relieved by the customary treatment and who therefore find life all but intolerable In many of these angina is the sequel of serious myo-

cedure is the provision of vasodilation One means to this end may be oral administration of xanthine compounds e g theobromine calcium salicylate (7½ gr 0 5 Gm) or theophylline with ethylenediamine, i e aminophylline (3 gr , 0 2 Gm), four times a day Both drugs are best tolerated when enterically coated, however since the coating does not always dissolve coated tablets are sometimes ineffective Caffeine, although a purine vasodilator should be avoided because of its cerebral action and its use as coffee should be limited Alternatively papaverine (3 gr , 0 2 Gm) may be given orally three or four times a day It depresses ventricular excitability and may lessen one source of the patient s anxiety namely, extrasystoles Its general usefulness is controversial Vasodilator tissue extracts have been tried but the effect is uncertain and the demands on physician and patient by daily injection are onerous Testosterone intramuscularly (as propionate 25 mg) three times weekly has been effective in some males However the expense may weigh heavily on those already greatly burdened It is not clear whether its action is one of vasodilation of hypogonadal relief or a direct action on the cardiac muscle as part of its claimed systemic tonic action

The attack —The physician having taken measures which prevent vasoconstriction and promote vasodilation must ordinarily leave actual treatment of the attacks to the patient The patient *should know that he must rest during the attack He is given* a vial of nitroglycerin tablets The more soluble hypodermic tablets are preferable the dose is 0 3–0 6 mg (1/200–1/100 gr) sometimes less and is selected by the patient s response when he dissolves the tablet under his tongue during an attack The tablet is used whenever an attack impends or occurs or when an unavoidable situation arises which the patient knows may provoke one A more rapid but somewhat less tasteful effect is secured by inhalation of amyl nitrite (0 12–0 18 cc) from a glass perle crushed in a handkerchief A timid patient is usually prevented from excessive dosage

must be given with the diagnosis of hypertension and angina. The general explanation of hypertension we have suggested. Regarding angina the patient may be told that it is the warning cry of the heart for blood and that the needed blood will be supplied by the treatment to be given him The importance of preventing or abort ing attacks by rest and nitrites should be clearly stated. He must realize that he is largely responsible for the success of the treat ment the drugs which will prevent or dispel attacks are placed in his hands it is then his problem *to restrict effort* and to lessen and avoid the occasions of emotional *tension* If there is evidence of serious myocardial or coronary arterial disease with the probability of a fatal seizure some excuse such as that it is a disturbing provo cation can be found to keep the patient from driving his car In prognosis the example of John Hunter may be used He had angina for 20 years complicated by infarction during some part of its course and died in a seizure because he failed to control his temper

The prognosis should be more objectively explained to the nearest interested relative Although the average duration of life after the first attack is commonly considered to be five years White Bland and Miskall have shown that the time is now almost doubled—to an average survival of nine years Ten per cent of their patients survived 18 years or more These data are compiled from observations in both normotensive and hypertensive patients There are many evidences that hypertension and cardiac hyper trophy shorten the t rm

Acute Coronary Insufficiency Coronary Failure

Acute coronary insufficiency or co onary failure is a state of inadequate coronary perfusion in which pain or other distress per sists longer than in angina pectoris which may be associated with foci of necrosis in the myocardium but which does not cause frank acute myocardial infarction This state is qualitatively different from

cardial infarction The surgical procedures aimed at their relief (*a*) may be intended only to cut the pathways of pain and include upper thoracic sympathetic ganglionectomy and paravertebral injections of alcohol, or (*b*) may reduce cardiac demand by thyroidectomy or (*c*) may be directed to formation of new cardiac collateral circulation Alcohol injections too often result in a trying neuritis Thyroidectomy is all but discarded Unilateral surgical cervical sympathectomy has been shown to be effective when the pain is lateralized Bilateral or substernal pain can be treated by bilateral upper thoracic section of the nerve roots The patient should understand that the masking of pain should not tempt him to untoward activity These procedures demand special skill in execution and experience in the selection of cases Operations on the heart are more hazardous and are definitely experimental Their aim is to restore a larger coronary blood flow by increasing inter and extra coronary anastomoses Among these the procedure of Beck, which turns a peripheral artery into the coronary sinus is one of the most imaginative and it is to be hoped perhaps to be the most successful The surgical treatment of angina has been reviewed in detail by White and Smithwick by Feil, and editorially in *Annals of Internal Medicine*

Radioiodine (I^{131}) has been used recently to induce a state of hypothyroidism which has been found beneficial in a small group of patients with intractable angina (Blumgart *et al*)

Finally, there is the question of what to tell the patient He will almost certainly have guessed the diagnosis and will have found that lay writers on medicine have done much to make it terrifying It is not advantageous to conceal the diagnosis beyond the time when the course of orderly examination permits a full evaluation of his condition Katz suggested that the term coronary insufficiency be applied to both angina pectoris and coronary occlusion in discussions with the patient It is a justifiable phrase and is not intrinsically frightening When that time comes some explanation

TABLE 8.—DIFFERENTIATION OF ANGINA PECTORIS, CORONARY INSUFFICIENCY AND CORONARY OCCLUSION (cont.)

	Angina Pectoris	Acute Coronary Insufficiency	Coronary Occlusion
Circulation			
1. *Shock*	*None*	May be present	*Common*
2. Blood pressure	No change or rise	Falls	Falls
3. Heart sounds	No change	*May be poor*	Embryocardia, gallop, pericardial rub
4. Arrhythmias	None	Occasional	Common
5. *Heart failure*	*None*	May be present	Common
6. *Fever*	Absent	Frequently absent	*Present*
7. Sedimentation rate	Normal	Frequently normal	Abnormal
ECG	*Usually no change*, evanescent RS-T depressions	RS-T depressions and T wave changes for several days or weeks, no Q waves or RS-T elevation	RS-T elevation, Q waves, leads I and III, *reciprocal progressive pattern*, often permanent
Duration of *incapacity*	*Minutes to few hours*	Several hours or weeks	Prolonged
Prognosis	Good	*Usually full recovery*, occasionally fatal, often depends on precipitating factor	Usually permanent symptoms, often fatal

TABLE 9.—DIFFERENTIATION OF ANGINA PECTORIS CORONARY INSUFFICIENCY AND CORONARY OCCLUSION (MASTER JAFFE DACK AND GRISHMAN)

	Angina Pectoris	Acute Coronary Insufficiency	Coronary Occlusion
Physiology	Ischemia transitory (inadequate coronary circulation)	Ischemia severe or prolonged (inadequate coronary circulation)	Total cessation of coronary flow in obstructed artery
Pathology	1 Coronary arteries sclerosis and narrowing 2 Myocardium no acute changes	Variable degree of sclerosis or normal sclerosis necrosis—small diffuse areas subendocardial papillary muscle no pericarditis no mural thrombosis	Sclerosis occlusion by thrombus or intimal hemorrhage in farction — large confluent endo- myo and pericardial pericarditis common mural thrombosis with embolization common
Predisposing factors	Coronary sclerosis hypertension aortic stenosis and insufficiency Graves disease anemia syphilitic ostial stenosis	Coronary sclerosis hypertension aortic stenosis cardiac enlargement anemia syphilitic ostial stenosis	Coronary sclerosis hypertension
Precipitating factors	Effort emotion cold eating trauma reflex from other viscera tobacco insulin and epinephrine	1 Similar to angina pectoris 2 Acute conditions with anoxemia Hemorrhage shock or fall in blood pressure sudden rise in blood pressure tachycardia heart failure infections trauma operation and anesthesia	None Operation (?)
Pain	Temporary relieved by nitroglycerin	Variable often absent	Prolonged not relieved by nitroglycerin

DAVIS D AND KLAINER M. J Studies in hypertensive heart disease I The incidence of coronary atherosclerosis in cases of essential hypertension, Am. Heart J 19 185 1940
——— II. The role of hypertension per se in the development of coronary sclerosis ibid. 19 193 1940
——— III Factors in production of angina pectoris ibid. 19 198 1940
——— The development of the concept of hypertensive heart disease New England J Med 224 679 1941
DEARING W H. ESSEX, H E HERRICK, J F., AND BARNES, A. R. Experiments with calculated therapeutic and toxic doses of digitalis Am. Heart J 25 719 1943
Editorial Surgical measures for the relief of intractable anginal pain Ann. Int. Med. 29 379 1948
ERNSTENE, A. C. Coronary Heart Disease American Lecture Series (Springfield Ill Charles C Thomas Publisher 1948)
FARBER, E. M HINES E A., JR. MONTGOMERY H., AND CRAIG W M. The arterioles of the skin in essential hypertension J Invest. Dermat. 9 285 1947
FEIL, H Clinical appraisal of the Beck operation Ann. Surg. 118 807 1943
FENN G K. Angina pectoris M. Clin. North America 28 16 1944
FREEDBERG A. S BLUMGART H. L. ZOLL, P M., AND SCHLESINGER, M. J Coronary failure J A. M. A. 138 107 1948
HERRICK, J R. A Short History of Cardiology (Springfield Ill. Charles C Thomas Publisher 1942)
KERR W J Angina pectoris Etiology and treatment, Texas State J Med. 3 711 1942
KOUNTZ, W B AND SMITH J R. The flow of blood in the coronary arteries in pathological hearts J Clin Investigation 17 147 1938
LESSER, M. A. The treatment of angina pectoris with testosterone propionate New England J Med. 228 185 1943
MAJOR R. H. Classic Descriptions of Disease (2d ed Springfield Ill. Charles C Thomas Publisher 1939)
MASTER, A. M. JAFFE, H. L. DACK, S AND GRISHMAN A. Coronary occlusion coronary insufficiency and angina pectoris A clinical and post mortem study Am. Heart J 27 803 1944
MURPHY F D WOODS R. M. AND GRILL, J Hypertensive heart disease—its clinical pathological manifestations Minnesota Med 20 627 1937
WHITE J C. AND SMITHWICK R. H The Autonomic Nervous System Anatomy Physiology and Surgical Application (2d ed. New York The Macmillan Company 1941)
WILLIUS F A AND KEYS T E. Cardiac Classics (St. Louis C. V Mosby Company 1940)

II MYOCARDIAL INFARCTION AND CORONARY THROMBOSIS

Coronary atherosclerosis latent or evidenced by angina pectoris or congestive failure may be complicated by thrombotic occlusion whenever the conditions for intravascular clotting

angina pectoris in that it is often associated with death of myocardial tissue, it differs from coronary occlusion with myocardial infarction in that the completion of major arterial occlusion is not the proximate precipitating factor In terms of severity and prognosis, it is intermediate between angina and infarction The designation is useful insofar as it includes a group of obscure, sometimes ill defined conditions and indicates the general approach to their treatment

Table 8 presents a differential description of this condition, angina pectoris and coronary occlusion In forming the diagnosis attention is directed particularly to the mode of onset in which there is usually a definite precipitating factor whose presence may overshadow the associated cardiac pain Subsequently, the presence of myocardial necrosis may be indicated by fever leukocytosis and elevation of sedimentation rate although these phenomena are not nearly as common or as severe as in major cardiac infarction The electrocardiographic changes are more characteristic These are limited to S–T depressions and T wave inversions in two or more leads, this pattern is not usually as fleeting as it is with angina or as persistent as in severe left ventricular strain The changes differ from the S–T elevations and Q wave formation which characterize coronary occlusion with infarction

In the acute stage of the illness treatment is essentially that of coronary occlusion of which the acute coronary insufficiency may be a precursor Morphine may be unnecessary shock is not present, neither cardiac rupture nor cardiogenic embolization is likely Return to restricted activity begins about 10–14 days after the attack It is customary to prescribe some form of theobromine or theophylline in 0 3–0 5 Gm doses four times daily for several weeks

BIBLIOGRAPHY

Blumgart H L Freedberg A S Kurland G and Ureles A L Treatment of intractable angina pectoris and congestive failure in euthyroid patients by producing hypothyroidism with I131 Tr A Am Physicians 1949 50 (to be published)

wall of the left ventricle and anterior interventricular septum In contrast two branches contribute to infarction of the posterior left ventricular wall and septum the circumflex branch of the left and the terminal branches of the right coronary artery Individually neither channel is occluded as often as the anterior descending artery but the sum of the frequencies of their occlusions lead to an almost equal incidence of posterior and anterior ventricular infarction

The area of infarction sometimes does not correspond to the distribution of a single normal arterial branch Such irregularly disposed infarcts may result from occlusion of a collateral vessel stimulated to function by prior occlusion of a normal vessel Except in young persons it is safe even when the infarction corresponds to normal arterial distribution to consider that occlusion of more than one artery participates in its formation

Coronary thrombosis may occur without infarction and myocardial infarction commonly results from some restriction of oxygen supply other than that of occlusion The compound term myocardial infarction due to coronary artery occlusion best describe the condition although major arterial occlusion and infarction ar all but synonymous among most patients with hypertension Th term coronary infarction is meaningless

Clinical Description

That myocardial infarction due to coronary occlusion migh exist as a syndrome as well as a cause of sudden death was all bu overlooked until between 1912 and 1920 James B Herric brought to it the attention it deserves He had precursors of cours The development of the concepts of coronary disease is modest told in his *History of Cardiology* and in a subsequent account his own contributions As Osler wrote of Holmes and childbe fever It is not the *man* who first says a thing but it is he who sa it so long so loudly and so clearly that he compels men to he

namely slowing of the stream of blood and endothelial denudation, are fulfilled Flow is slowed by sclerotic obstruction and increased tissue pressure due to increased systolic efforts, the endothelium may degenerate over an atheroma forming an ulcer (about 40 per cent of cases) or may be suddenly burst by hemorrhage in the vascular base of a sclerotic area (about 60 per cent) Fibrin forms on the denuded site blood cells are enmeshed and the clot grows to occlude the vessel In a degree which depends on the presence of former occlusions the patency of old or the availability of new collateral channels, occlusion robs a discrete mass of muscle of its blood As with vascular occlusions elsewhere the neighboring channels of arterial supply are probably thrown into reflex spasm which exaggerates the deficiency of blood flow But reflex spasm seems to be much less significant a factor in rapid death after myocardial infarction than increased irritability of the ischemic muscle which predisposes to ventricular fibrillation (Opdyke and Selkurt) The central zone of the ischemic area undergoes infarction (Lat *infarcire* to stuff in) with necrosis in the center and peripheral zones of hemorrhagic exudate (the stuffing) and hyperemia peripherally during the first week According to the site and mass of the infarct the heart action is temporarily or permanently embarrassed The infarct is invaded by granulation tissue and exudate Absorption of the necrotic muscle and resolution of exudate are followed in about six weeks by formation of fibrous scar Meanwhile collateral vascular channels have been formed and the site of obstruction may itself be recanalized but the new channels are less effective than their normal predecessors because they are smaller and carry a lower head of pressure

The sites of atherosclerotic predilection on which occlusions form lie at points of branching Branches of the major arteries rather than the main channels are thus the most frequent sites of occlusion The branch most often affected is the left anterior descending artery Its occlusion results in infarction of the anterior

enced by the obstruction and by the ability of the remaining vessels properly to carry on their work as determined by their health or disease No simple clinical picture of the condition can therefore be drawn. All attempts at dividing these clinical manifestations into groups must be artificial and more or less imperfect Yet such an attempt is not without value as it enables one the better to understand the gravity of an obstructive accident to differentiate it from other conditions presenting somewhat similar syndromes and to employ a more rational therapy that may to a slight extent at least be more efficient. Thus wrote Herrick in 1912

Death may be immediate and painless or delayed a few minutes and agonizing survival may be for days months or years pain may be severe and the symptoms insignificant or the disturbance profound and pain hardly felt. These are a few of the variants The typical pattern is that of a group whose symptoms are severe are distinctive enough to enable them to be recognized as cardiac, and in which the attack is usually fatal but not immediately and perhaps not necessarily so (Herrick) Usually and perhaps in the last sentence have been modified as recognition has increased and treatment improved. The present mortality rate is estimated at from 10 to 30 per cent

The attack may occur at any time of the day or night Unlike angina pectoris there is no immediate association with exercise Indeed exercise seems to speed blood flow and postpone the completion of a clot and rest, which slows flow may permit occlusion Sometimes a history is obtained of unusual exertion which precedes by a day or two an attack which comes on during sleep In such cases it is conjectured that the strain of exertion has sheared off the weakened endothelium over an atheroma or caused hemorrhage into its base and that the slower circulation of sleep allows the clot to become complete More often no immediate precipitating factor can be found

Still since the final occlusion depends on a clot, which may

him, it is to him that the credit belongs So it may be said of Herrick and coronary thrombosis

Rapidly increasing recognition of the syndrome brought to light the *enormous problem of an affliction which strikes down* vigorous men, more than twice as often as women, and in the prime of useful life Nearly half the deaths from heart disease are now related to coronary arterial occlusion, in 1925 less than a third of cardiac deaths were attributed to any form of coronary disease and occlusion was considered rare Estimates of the frequency with which hypertension precedes occlusion vary from 20 to 80 per cent *It is all but certain that hypertension predisposes to it, for* as with angina coronary occlusion rarely occurs in women in the absence of increased arterial pressure diabetes or other defect predisposing to atherosclerosis

Predisposing factors are those of atherosclerosis three of these —advancing age, masculinity and hypertension—we have noted The others, though hardly less definite, are not as clearly understood *Obesity probably doubles the likelihood of coronary* occlusion The general impression is that incidence is most frequent among heavy set muscular males A concomitant personality pattern which differs in detail from that of essential hypertension has been described The psychologic points of difference are believed to lie in the greater tendency of those with coronary disease to project their emotions so that they strive and dominate are articulate and companionable and overwork toward a planned future The group therefore includes at any level of income and social status those who tend toward larger shares of achievement income and education The manifestations of the disease are more severe in sensitive mentally overworked and frequently robust or stout professional and business men than in other individuals (White)

The clinical manifestations of coronary obstruction will evidently vary greatly depending on the size location and number of vessels occluded The symptoms and end results must also be influ

tation rate The beat ceases in the infarct so that it forms a passive component of the ventricular wall which by roentgenkymography or fluoroscopy may be seen to dilate in systole

The infarct may extend to the epicardium A deposit of fibrin then forms on the surface and especially when it is anterior causes a friction rub which appears in about 24 hours and lasts for hours or days When the infarct causes necrosis of endocardial endothelium fibrin is deposited from the blood This mural thrombus is at first loose and weak in mesh since it encloses many cells thus it breaks easily and gives rise to emboli which since the infarction occurs most often in the left ventricle pass into the systemic arteries The resultant embolization appears in the brain spleen or kidney or less commonly in the limbs where the volume of blood flow is smaller When the cardiac symptoms were slight or disregarded the symptoms of embolization may first attract attention to the underlying disorder

THE ELECTROCARDIOGRAM

The electrocardiogram is of great importance in the diagnosis of myocardial infarction since its pattern is characteristic in more than nine cases out of 10 The principal changes occur in the Q S and T waves and S–T segments They are usually recorded in opposite directions from the isoelectric line in leads I and III The patterns evolve through one of recent infarction present within a few hours and lasting for two to four weeks to one of late infarction and thence to the abnormalities of healed infarction Lead I and chest leads are greatly affected by electrical events on the anterior surface of the left ventricle so that the more conspicuous changes of anterior infarction appear in their records Posterior infarction is indicated chiefly by changes in lead III The variations of these patterns or in certain cases the absence of electrocardiographic changes in standard limb leads have led log

form slowly in the lumen manifestations of its presence may precede its completion These are found retrospectively in 40 or 50 per cent of cases to be present within the 24 hours or even the two weeks before the attack Cardiac pain is the most common, although *dyspnea and palpitation may* occur The pain has the distribution of angina pectoris and may occur at rest and pass off with exertion This is one of the pains the patient walks off These signs and symptoms are in fact almost identical with those of coronary insufficiency or acute coronary failure (p 173) The sudden onset of any untoward cardiac manifestation in a patient whose build and age make him liable to coronary arterial disease may be a warning of impending occlusion Unfortunately these precurrent symptoms are rarely premonitory (Lat *praemonere,* to warn before) in the sense that they are recognized for what they are by patient or physician

Consequently all but a few patients are first seen after final *occlusion Pain is present in all but 3 or 4 per cent of those who* live to tell their story Its character and distribution are those of angina pectoris from which it differs in that it is prolonged rarely relieved by rest does not fully respond to nitrites and is slowly relieved by morphine It is limited to the upper abdomen in 2.4 per cent of cases Like anginal pain it is presumed to arise from accumulation of metabolic products around nerve endings which in this *instance lie at the margin of the infarct* The afferent autonomic stimuli also set off reflexes Locally they cause vasoconstriction and systemically cause vomiting gastric and intestinal distention transitory hyperglycemia and glycosuria The familiar clinical features (syncope feeble heart sounds initial shock hypotension changes of *rate and rhythm dyspnea congestive failure pericarditis embolization* electrocardiographic abnormality) which attend and follow the attack derive from the presence within the heart of necrotic tissue causing fever leukocytosis and increased sedimen

COURSE

The effect on arterial pressure varies The cardiac injury may cause it to fall greatly at the onset, and shock may appear In a hypertensive patient a fall of systolic pressure to 90 mm. Hg is unusual and ominous Commonly in the absence of prolonged shock or severe congestive failure the pressure rises in 48 hours to its preinfarction level and a secondary moderate decrease appears in 12–20 days The pressure may remain at this decreased level or in some two thirds of patients be restored to the original level within weeks or months Most of those whose pressure does not return to its former level suffer from marked myocardial damage are dyspneic in failure and bedfast A very few are not, but rather seem improved. In these it may be inferred that the prolonged decrease of blood pressure has somehow decelerated the activity of the hypertensive state

Shock, congestive failure and the onset of ventricular fibrillation or embolization from a mural thrombus may cause death during the first week Near the end of this time the ventricular wall may soften and burst. This occurs in about 5 per cent of fatal cases it is three times as likely when hypertension is present and persists after infarction and is less likely in the presence of hypertrophy or when the scar of previous infarction thickens the wall Thinning of the wall which probably predisposes to rupture and later results in cardiac aneurysm has been experimentally shown to follow exercise during the first week after coronary ligation The organization of the scar is nearly complete at about the eighth week although further recovery of myocardial function may be expected. Between the first and the eighth week pulmonary embolization may occur from saphenous femoral or iliac thrombi arising on the basis of immobilization slowed circulation and the "thrombotic diathesis" of certain patients The hazards of sudden death and of repeated infarction persist

ically to widespread use of semidirect (chest esophageal) leads These are often more accurate in their localization of infarcts because they record the impulses from points close to the heart and the site of injury

The record may also be used to establish *the nature of an accompanying abnormality of electrical mechanism* As with other electrocardiographic changes, the patterns of infarction are more surely interpretable when a previous record is available for comparison The use of multiple precordial leads and the direction of technic and interpretation of records by one skilled in them will resolve *most problems of difficult diagnosis The anatomic accuracy of electrocardiographic prediction is* about 95 per cent

Among abnormalities of conduction and excitation which may appear in the electrocardiogram the more important are heart block auricular fibrillation alternation and ventricular extrasystoles which proceed at times into ventricular tachycardia from which *fatal ventricular fibrillation develops* Ventricular tachycardia should be suspected when the heart rate suddenly becomes rapid (180–200 per minute) while fundamentally regular and unresponsive to carotid pressure

Diagnosis

This illness is now widely recognized We need not delay to summarize clinical and laboratory data and the observations which establish it Conditions such as pulmonary embolization pericarditis aortic dissection pneumonia herpes zoster and acute upper abdominal disease may temporarily simulate some of the aspects of infarction Pain alone possibly fright may give rise to abnormalities of T wave and S–T segment but not to characteristic abnormalities of the QRS waves *If the diagnosis is* uncertain it is much better to err on the side of safety (Gilbert) *This is especially* true in the treatment of a hypertensive suspected of *having* myocardial infarction

40 per cent were the result of recurrent infarction 35 per cent were sudden and attributed to ventricular fibrillation 20 per cent were due to progressive congestive failure The more severe the initial attack the longer its manifestations took to subside the more likely was the evolution of myocardial infarction into a course of con gestive failure severe angina and greatly restricted activity The patient may be heartened by numerous accounts of survival of 20 years and more and especially by a 10 year survival in 25 per cent of a group studied by Bland and White The presence of hyper tension may shorten the estimated life expectancy

Shoulder pain on the left more often than the right with weak ness and limitation of movement usually with evidences of reflex sympathetic dystrophy in the hand may follow an attack by weeks or months This complication which occurs in about 15 per cent of patients should be recognized as such and not attributed to recur rent infarction

Treatment

The treatment of myocardial infarction falls into three phases (1) *prevention* (2) treatment of the acute attack in its typical pattern and its complications and (3) treatment at the third or fourth week with attempts directed toward restoration to as active a life as seems desirable These phases correspond respectively to the prevention of sclerosis the relief of pain and thwarting of death and the promotion of a firm myocardial scar surrounded by healthy tissue which is nourished by adequate collateral vessels With due regard to improvements in treatment, it seems likely that the im proved prognosis of this state over Herrick s early estimate is partly attributable to the diagnosis of mild cases

Prevention—Preventive treatment must for a time remain a matter more of guess and resolve than of undisputable accomplish ment It consists of attempted control of hypertension overnutri tion and other predisposing states Should premonitory symptoms

Prognosis

Immediate mortality increases with advancing years repeated attacks and pre existing hypertension It is therefore greater in women in whom infarction is usually associated with hypertension and advanced age A history of angina pectoris is favorable, possibly because the ischemia of angina stimulates the formation of collaterals The painless infarct, in which pain is obscured by shock or cardiac failure is usually fatal Mortality increases from 18 per cent in patients without dyspnea to 62 per cent in those in whom it is severe while the degrees of shock and cyanosis similarly parallel mortality The degree of necrotic absorption indicated by fever and leukocytosis is significant, mortality was 16 per cent in those whose leukocyte count did not exceed 15 000 and 54 per cent in those with higher counts To these unfavorable factors may be added the persistence of pain for more than 12 hours and of fever and leukocytosis for a week or more rapid and marked cardiac dilatation protodiastolic gallop rhythm ventricular paroxysmal tachycardia heart block pulsus alternans pulmonary edema with or without cardiac asthma dropsy and embolic phenomena The commonest cause of death in this phase is congestive failure

The prognosis after healing is more difficult to evaluate The mean duration of life in one group (Rosenbaum and Levine) was 44 months and the median about 25 months Angina persisted or appeared in two thirds of the group In a few who were previously subject to it angina disappeared presumably because nerve endings in a formerly partially ischemic zone were now destroyed Congestive failure appeared in half the group Despite these disabilities about three quarters were restored to full or partial activity, the larger proportion was composed of those whose infarcts were posterior Women in contrast to men lived shorter lives maintained less activity and more often developed congestive failure Nearly all (95 per cent) of these patients deaths were from cardiac causes

sue in which its retention had made it seem ineffective In such situations it is probably better to give a small dose (1/8 or 1/12 gr 8 or 5 ½ mg) intravenously Atropine (1/75 gr 0 8 mg) is given subcutaneously with the first dose of morphine A coronary vasodilator either papaverine (½–1½ gr 30–90 mg) or theophylline with ethylenediamine (3¾–7½ gr 0.24–0 48 Gm.) is given slowly intravenously through a 25 gage needle withdrawing blood into the syringe from time to time and controlling the rate by ceasing injection when the pulse speeds or weakens

If the patient is not there already he should be put to bed preferably in a Gatch bed. An ordinary bed is provided with back and knee rests and the head raised on a chair or blocks of wood. Once there whether in the hospital or at home he should not be moved under circumstances short of fire for three weeks

Oxygen is brought to the bedside dyspnea pulmonary congestion Cheyne Stokes respiration cyanosis shock or untoward cardiac rhythms are indications for its use in concentrations of from 50 to 100 per cent. The lower range of concentrations (50–75 per cent) may be secured comfortably by a tent or more rapidly by a nasal catheter inserted into the oropharynx The use of a catheter requires application of a surface acting local anesthetic ointment in its track through the nostril lubrication and removal of the catheter and re insertion in the opposite nostril once in 24 hours The most satisfactory device is the oxygen mask Severe symptoms require the use of 100 per cent oxygen for which the mask is the most practical means with the gas delivered at a rate of 12–15 L. per minute The absence of cyanosis does not indicate that oxygen is useless Barach observed Even though the oxygen saturation of arterial blood may be normal it should be borne in mind that the inhalation of 100 per cent oxygen is accompanied by a significant increase in the physically dissolved oxygen of the arterial blood leading to the collaterals of the occluded blood vessel This results in a substantial increase in the pressure of oxygen available to the heart muscle

appear, bed rest is desirable, not because it will prevent the developing occlusion but because the supervision it implies should enable the physician to limit the effects by immediate treatment Controlled administration of anticoagulants such as heparin and dicumarol® might stave off threatened thrombosis But these are two edged swords since the intimal hemorrhage on which occlusion so often depends may be increased when coagulation is inhibited Papaverine (3 gr, 0 2 Gm) three to four times a day orally may be given as a vasodilator and inhibitor of ventricular irritability, and atropine (1/75 gr, 0 8 mg) three times a day subcutaneously as an inhibitor of reflex vasoconstriction Although experimentally indicated neither procedure is clinically established However, since it will remain impossible to prove the advantage of procedures aimed at preventing imminent myocardial infarction the logic of the situation demands a routine of rest and appropriate medication

The acute attack—The attack and its treatment may be considered as carrying through the first three weeks Too often early treatment is delayed because the physician uncertain of the diagnosis, fears to alarm the patient or even when sure of his ground believes that bed rest and nursing care are all that can be done (Gilbert) In some cases the diagnosis must at first be obscure The physician whatever his feelings should present himself as easy quiet confident neither indifferent nor alarmed Although he must know that he cannot abolish an occlusion by acting quickly he can do much to control its consequences

IMMEDIATE MEASURES Morphine (¼ gr, 16 mg) subcutaneously is usually the first drug given and is repeated at intervals of 30 or 60 minutes as necessary for pain for three or more doses Shock with feeble peripheral circulation and some dulling of the sense of pain demands that less be given This is because the restored circulation which follows relief from shock may disastrously pour into the veins a pool of morphine from the subcutaneous tis

The sum of the evidence gathered is that the hazards of the use of anticoagulants do not contraindicate their administration when satisfactory serial measurements of prothrombin time can be made and that with this safeguard and with adequate dosage the use of dicumarol[*] greatly reduces the incidence of thromboembolism and definitely decreases mortality It is of course contraindicated in the presence of hemorrhagic diatheses The fact that 23 deaths have been attributed to dicumarol[*] suggests that it should be used with caution in patients with severe hypertension and a history of cerebrovascular accidents Still the broad experience of Wright, Allen Barker and Nichol shows that it can be used to advantage even in very serious circumstances and that under proper safeguards it is comparatively harmless

Since dicumarol[*] does not have an immediate effect anticoagulant treatment is usually started by giving enough heparin intravenously to bring clotting time to 30–45 minutes (when normal time is up to 10 minutes) Dicumarol[*] is given in a dose of 300 mg orally the first day The prothrombin time is measured the next day *before the* second dose is decided on Usually the second dose will be 200 mg and this will be repeated daily to maintain prothrombin time in the range of 30–35 seconds (Link Shapiro method normal 15–17 seconds) An additional 50 or 100 *mg* may be required to reach this level Dosage is decreased or suspended when the time is greater than 35 seconds There is no immediate need for treatment by transfusion and vitamin K (60–75 *mg* intravenously every four hours) unless the prothrombin time exceeds 50 or 60 seconds The customary treatment is merely to hold off further dosage until the prothrombin time reaches 30 seconds when the amount to maintain the level between 30 and 50 seconds is decided on as 50 100 or 200 *mg* depending on previous responses

The aim in scheduling dosage is to maintain prothrombin time between 30 and 50 seconds during the three to four weeks in which thromboembolism is to be feared

which may maintain the function of the circulation as a whole even in the presence of a considerable area of infarcted and functionless cardiac muscle In severe cases oxygen treatment should be continued for approximately five days after onset of the attack Overbreathing as from pain, may cause loss of carbon dioxide and a tendency to alkalosis which in turn sensitizes vessels to constriction This hyperpnea may persist when oxygen is used A carbon dioxide deficit due to overbreathing is evidenced by decreased plasma content of carbon dioxide and alkalinization of the urine It is countered by administering low concentrations (2–5 per cent) of carbon dioxide with oxygen

ANTICOAGULANT TREATMENT The discovery of dicumarol® was fascinatingly told by Karl Link in the Harvey Lectures of 1943–44 From its first isolation it was obvious that the drug would serve in the treatment of primary thromboembolic disease Several clinicians later independently developed the view that it might prevent thromboembolic complications of myocardial infarction In 1 605 cases in the literature Hellerstein and Martin estimated the incidence of such complications as 11 5 per cent But evidently as a result of increased awareness and more searching examination they found an incidence of 45 per cent in 160 cases of their own In order of frequency the sites of embolization are the lungs kidneys spleen extremities and brain In general it is conceded that these complications account for about 20 per cent of deaths *from myocardial infarction Consequently* their prevention should in theory do much to reduce disability morbidity and mortality

The problem could not be answered by scattered studies of small groups of patients Consequently under the aegis of the American Heart Association *a group of investigators headed by Irving Wright* set to work on a statistically sound clinical trial aimed at evaluating the advantages requisites and dangers of dicumarol® treatment in patients with myocardial infarction

isolation may do harm by causing anxiety The skilled nurse is perhaps the best judge of the good or hurt they may do Complete mental relaxation bordering on drowsiness is obtained by morphine given only *when pain persists* or by hypnotics such as amytal * pentobarbital (1½ gr 0 1 Gm) phenobarbital (¾ gr 0 05 Gm) or chloral hydrate (10 or 15 gr , 0 65 or 0 98 Gm) three times a day separately or in alternation Alcohol in some agreeable form neither iced nor in carbonated waters contributes to relaxation and in small doses (½–1 oz) three or four times a day may substitute for other sedation Coffee is given only in caffeine free forms Smoking is forbidden

The diet at first should be liquid provided every four hours as broth milk or fruit juice (not iced) and after a few days soft as custard apple sauce cooked cereal (neither hot nor cold) and never given with insistence An intake of about 1 500 calories is adequate Fluid intake is maintained at 2 500–3 000 cc daily There is nothing to show that any reasonable volume of swallowed water can be a load on the heart except by reflexes which a large volume of iced water can release from the stomach The discomfort of dehydration is an avoidable burden

Distention apart the bowels need not be considered for two or three days A 1 or 2 oz. oil or glycerin enema is then given and repeated as necessary All patients should use the bed pan those who make hard work of it may be moved to a commode beside the bed for evacuation of the bowel After 48 hours a gentle laxative (cascara, mineral oil and agar milk of magnesia) may be prescribed daily

The regime is best secured through careful skilful professional nursing Special care should be continued at least two weeks

COMPLICATIONS A common complication of the early course is abdominal distention Since it decreases coronary blood flow it may be dangerous as well as uncomfortable Heat to the abdomen turpentine stupes and insertion of a rectal tube may relieve it When

THE FIRST DAYS Morphine is continued as necessary for pain Reflex ectopic rhythms may be inhibited by atropine (1/150 gr, 0 4 mg) given at four, six or eight hour intervals in the first 24 or 48 hours Vasodilation is stimulated by repeated perhaps alternating use of papaverine (3 gr, 0 2 Gm) orally three to four times a day or (1½ gr, 0 1 Gm) intravenously every three or four hours or aminophylline (3¾ gr, 0 25 Gm) intravenously every four hours The two drugs should not be given at the same time but may be given one or more hours apart The dosage of atropine is decreased in the presence of tachycardia and discontinued when the patient's condition seems stabilized that is, at about 48 hours Papaverine and aminophylline may be continued Of the two papaverine because it acts as a vasodilator and a ventricular depressant may be the more useful If it relieves pain, it may substitute for quinidine (3 gr, 0 2 Gm orally every six hours) which also inhibits the abnormal ventricular rhythms which go on to fatal fibrillation Complete auriculoventricular block rarely present, is a presumptive contraindication to the intravenous use of papaverine No obvious benefit may be observed from use of these vasodilators Still the need of the heart for blood is so great and their value so convincing experimentally that we would continue their use

LATER DAYS Although the emergency of the first two or three days may pass without complications the aims and modes of treatment are little altered The physician's purpose is (1) to reduce to a minimum the demands on the heart, (2) to encourage collateral circulation and inhibit thrombotic spread and (3) to prevent and treat complications

The work of the heart is reduced by rest physical and mental The patient is given no occasion for unnecessary movement He is fed during the first week Nonessential examinations which require movement are left undone His visitors the immediate family and close friends are selected and instructed on their behavior which should not cause anxiety or any violent change of mood Complete

continued in 3 gr doses (0.2 Gm.) three times a day after meals It is not to be given intravenously or in the presence of severe auriculoventricular block. A synergism of quinidine with strychnine sulfate (1/40 gr 1 6 mg) may be useful particularly to control auricular fibrillation when given orally three times a day When quinidine and papaverine do not suffice magnesium sulfate (10–15 cc of 20 per cent solution) may be injected *intravenously the heart* rate serving as a guide to the volume and speed of the injection Potassium chloride (15 or 30 gr 1 or 2 Gm) every two or four hours orally may be given alone or with quinidine or papaverine Abnormal auricular rhythms unless they lead to tachycardia or congestive failure are not usually cause for concern Paroxysms of flutter or fibrillation which do not subside of themselves may be checked by quinidine (given in the manner described above) or digitalis

c) Congestive heart failure is most common just as occlusion is most ominous in older patients and in those who suffer from hypertension. An emergency may be tided over by venesection or bloodless phlebotomy The latter consists in application of blood pressure cuffs around the four limbs alternately brought to and released from diastolic arterial pressure Recent evidence indicates that induction of high caudal anesthesia may also trap blood in the veins below the level of the anesthesia and thus reduce effective circulating blood volume Oxygen is given (100 per cent 12–15 L. per minute) Glucose (50 cc of 50 per cent solution) may be administered intravenously every two or three hours Its value is questioned Mercurial diuretics reduce the blood and interstitial fluid volumes and thus decrease the load on the heart. Death, which results in a few rare cases from their intravenous injection is apparently due to ventricular fibrillation to which the patient with infarction is predisposed. Injection of 1 cc of 50 per cent magnesium sulfate with or just before the mercurial is claimed to lessen this risk (Pines *et al*) But, in view of the risks of intravenous injection

they do not suffice pitressin® should still be avoided, although the atropine like drugs trasentine® and novatrine,® may be used by in jection Hermann suggested the use of estrogen as estrone® (1 mg in oil) intramuscularly

The other complications of the early course are in order of frequency and time of onset (*a*) acute circulatory failure (*b*) arrhythmias (*c*) congestive failure and (*d*) embolization

a) Acute circulatory failure is expressed as shock and charac terized by dulling of consciousness, failure of cutaneous and pe ripheral blood flow indicated by pallor and cyanosis of lips and nail beds oliguria hypotension thready pulse and restlessness The syn drome as it appears after myocardial infarction seems to be due to failure of the heart to maintain its output and is in fact the pat tern of forward failure Shock demands the use of 100 per cent oxygen prevention of undue heat loss and elevation of the foot of the bed A hot room (over 85 F) or artificial heating may intensify the circulatory deficiency Hot water bottles are more dangerous than useful for the slowed circulation does not carry away their heat if the feet are cold let no busybody burn them A small transfusion of blood or plasma (150–200 cc) may be given intra venously at a rate of 4 cc per minute Theoretically this situation could best be met by intra arterial transfusion The value of this is under study Stimulation of myocardial glycogenesis has been the theoretical basis for the recommendation of infusion of 100 cc of 50 per cent dextrose Murphy recommended the concurrent infusion of aminophylline with the glucose solution

b) The more ominous arrhythmias are ventricular and consist of frequent premature systoles and ventricular tachycardia Both may be prevented by papaverine or quinidine Intravenous injec tion or large oral doses of papaverine may temporarily check them quinidine may be given orally after a test dose (3 gr 0 2 Gm) in doses of 6–15 gr (0 4–1 Gm) every three or four hours until the desired effect or toxic symptoms appear and if found useful

continued in 3 gr doses (0.2 Gm) three times a day after meals It is not to be given intravenously or in the presence of severe auriculoventricular block. A synergism of quinidine with strychnine sulfate (1/40 gr 1.6 mg) may be useful particularly to control auricular fibrillation when given orally three times a day When quinidine and papaverine do not suffice magnesium sulfate (10–15 cc of 20 per cent solution) may be injected intravenously the heart rate serving as a guide to the volume and speed of the injection Potassium chloride (15 or 30 gr 1 or 2 Gm) every two or four hours orally may be given alone or with quinidine or papaverine Abnormal auricular rhythms unless they lead to tachycardia or congestive failure are not usually cause for concern Paroxysms of flutter or fibrillation which do not subside of themselves may be checked by *quinidine* (given in the manner described above) or digitalis

c) Congestive heart failure is most common just as occlusion is most ominous in older patients and in those who suffer from hypertension An emergency may be tided over by venesection or bloodless phlebotomy The latter consists in application of blood pressure cuffs around the four limbs alternately brought to and released from diastolic arterial pressure Recent evidence indicates that induction of high caudal anesthesia may also trap blood in the veins below the level of the anesthesia and thus reduce effective circulating blood volume Oxygen is given (100 per cent 12–15 L. per minute) Glucose (50 cc of 50 per cent solution) may be administered intravenously every two or three hours Its value is questioned Mercurial diuretics reduce the blood and interstitial fluid volumes and thus decrease the load on the heart. Death which results in a few rare cases from their intravenous injection is apparently due to ventricular fibrillation to which the patient with infarction is predisposed Injection of 1 cc. of 50 per cent magnesium sulfate with or just before the mercurial is claimed to lessen this risk (Pines *et al*) But in view of the risks of intravenous injection

the slightly more uncomfortable intramuscular route is preferred If digitalis has been given, any tendency to intoxication from it should be excluded and its use suspended for a day before using the diuretic

Digitalis is not to be used routinely in infarction, those whose hearts are not dilated it may make worse It is given for congestive failure and for ventricular tachycardia due to auricular fibrillation which is leading to congestive failure The dose of powdered leaf is about 10 or 20 per cent less than would be given the patient had he no recent infarct The tradition that digitalis predisposes to ventricular rupture dies hard, it probably arose from the fact that the patients who most often require it are the most subject to this catastrophe Intravenous use of a cardiac glucoside demands special considerations detailed by various authors Belief that digitalis increases blood coagulability and predisposes to embolization is not satisfactorily proved

d) Emboli may be cardiogenic and ventricular, arising usually in the left ventricle by the fracture of a mural thrombus and causing arterial obstruction in the brain kidneys spleen or limbs alternatively, the thrombus may be auricular Such embolization is partly unavoidable The commoner source of emboli is a peripheral thrombus formed in a vein of the lower half of the body which obstructs a branch of the pulmonary artery This embolization is largely preventable The principal means of prevention is the controlled use of anticoagulants especially dicumarol® (p 190) Subsidiary means of prevention are measures which tend to prevent stagnation of blood in leg veins Immobilization with the back raised and the knees bent slows the blood flow in leg veins other positions may be difficult to maintain and the alternative of exercise of the limbs may jeopardize the heart The problem has been vigorously posed by William Dock whose distinguished father in 1896 was one of the first clinicians to make the diagnosis of myocardial infarction during life It resolves itself into selection of the lesser of two evils

The solution may lie in frequently repeated passive exercise of the legs during the first week keeping the feet and legs warm in the intervals and at about the second week the beginning of assisted active leg exercise and elevation. Massage may be helpful

Pulmonary embolization is probably made worse by the reflexes which the local arterial obstruction releases Atropine subcutaneously or intravenously and 100 per cent oxygen are given immediately on recognition followed by papaverine intravenously Pulmonary embolectomy is rarely an available procedure On the other hand peripheral cardiogenic embolization particularly of a large and accessible artery (iliac saddle thrombus of aortic bifurcation) is an indication for embolectomy The decision to operate depends on the skill of the surgeon and the possibility of controlled postoperative use of anticoagulants Embolization of leg arteries usually demands only paravertebral sympathetic block and the repeated use of papaverine

The drugs to be avoided during the first three weeks as unnecessary or harmful are those contraindicated in angina pectoris (p 171) with the probable addition of the nitrite vasodilators and active cathartics The transient hyperglycemia and glycosuria caused by the traumatic onset of infarction should not be confused with diabetes mellitus Infarction may be associated with acetonuria (disclosed by the nitroprusside test for acetone) and dyspnea and clouded consciousness due to circulatory failure It is differentiated from diabetic coma in part by feeling the axillae these in diabetic coma are dry

Late treatment —Early treatment shades into the later course at about three weeks The diet should now be established at a level of subcaloric (1 500–2 000 calories) nutrition with adequate palatable protein ration (1 Gm *per kg*) Vitamin supplements notably those of the B complex may be prescribed The drug treatment is by this time wholly oral Vasodilators unless especially indicated, may be discontinued. The duration of complete bed rest from four

through the classic six to eight weeks or more, depends somewhat on the apparent damage done by the infarct

Passive exercise and later active exercise of the arms and hands follows that of the legs this may prevent residues of stiffness in the shoulder joint and palmar contractures which may complicate the course at this time The response to such minor activity will aid in determining the time when the patient will be allowed out of bed and will give a clue to the future course A minimal convalescence of one or better two months is maintained after the patient is first allowed up The prolongation of this to three or six months, some of which is spent in a suitable spa under adequate medical supervision may be advised Thereafter noncompetitive pursuits and frequent vacations should be encouraged A return to stabilized normal activity without peaks and valleys is desirable It is not advisable for the patient either to travel or to live at high altitudes

A general psychotherapeutic orientation developed along the lines discussed in Chapter 7 should be begun That an encouraging but realistic prognosis should be given is obvious The patient will probably know that death may come suddenly It is the duty of the physician and family to aid the patient toward a point of view in which he does not feel with the poet *Timor mortis conturbat me* (The fear of death disquieteth me) Should the inaction and restraints seem too great or the proposed pattern of life intolerable minor overt psychotherapy may resolve the conflict which prevents the patient from doing what intellectually he is convinced he should

Persistent angina and congestive failure are treated along the lines recommended in the appropriate chapters They are indications for a greatly restricted diet such as that prescribed by Master Stricker Grishman and Dack One aim of the diet is to decrease physical demands and interests Another possible effect is the regression of atheroma By this means a comfortable life may be secured without risk Dietary restriction unless severe will have

little effect on patients whose actual weight approximates the ideal normal The presence of hypertension raises the problem of low sodium diets Until exact knowledge aids in selection of patients all of whom will respond to sodium restriction probably most patients would do well to complete their coronary convalescence by an adequate test of a low sodium diet (p 357)

Spontaneous Rupture of the Aorta

To a degree relatively greater than their increased liability to coronary occlusion hypertensives more often than normotensives are subject to aortic rupture Since this unusual condition may simulate coronary occlusion it is considered at this point.

Aortic rupture usually with extravasation of the blood directly through the aortic wall occurs in a few cases in the absence of atherosclerosis or hypertension or any easily defined local lesion The presumptive basis of such rupture is a congenital intimal defect the assumption is confirmed by a predisposition to rupture in aortic hypoplasia or coarctation.

Aortic rupture complicating hypertension is usually associated with atherosclerosis and in most cases with a *specific medial degeneration* called medial cystic necrosis The lesion consists of loss of muscle and elastic fibers and the formation of minute cysts which contain a mucoid substance Rupture in such cases is incomplete at the outset commonly it penetrates the adventitia *in a few days* A small proportion of these extravasations heal The incomplete extravasation forms what is known as dissecting aneurysm The lesion is so named because the *extravasation* splits the cystic media and penetrates the adventitia at a point *often distant* from the entering intimal tear It is not properly an aneurysm since its walls are not endothelial and clotting is *rapid* the lack of circumferential elastic tissue predisposes to penetration of the adventitia

Diagnosis—This is difficult, but with *increasing* recognition antemortem diagnosis is made in about 20 per cent of cases

The patient is usually a male who has hypertension The onset with tearing or crushing chest pain simulates myocardial infarction The pain of partial rupture is commonly severe and not readily relieved by morphine It differs from the pain of infarction in that it does not commonly radiate to the arms it radiates to the interscapular region and may travel down the back from the neck to the legs

The symptoms and signs are (1) those of extravasation (fever and leukocytosis) and (2) locally those caused by interference with circulation The local signs vary as extravasation progresses toward or away from the heart and from its more usual point of origin in the ascending aorta A cardiad direction leads to encroachment on the aortic ring so that sudden onset of aortic insufficiency with pain in the back or legs clearly indicates dissection A coronary artery may be occluded Such an extravasation is usually completed by rupture into the pericardium, with cardiac tamponade or into the mediastinum or pleura

Distally directed extravasation causes signs which vary with the arteries whose aortic mouths are compressed by the hematoma Carotid or innominate occlusion causes cerebral symptoms, innominate or subclavian occlusion marked asymmetry of arterial pressure The more common signs arise from obstruction of a renal artery with renal infarction and of arteries to the lumbar cord, with pain and partial or complete paraplegia

In contrast to myocardial infarction, the height of the blood pressure is maintained or sometimes increased and the heart while enlarged shows no weakness of sounds or characteristic electrocardiographic change The diagnosis may be confirmed by radiographic demonstration of suggestive distortions of the aorta or one of its branches

The prognosis at present highly unfavorable may lengthen into years as has that of myocardial infarction Minor so called silent dissections are thought to occur and even a clearcut syndrome may be followed by recovery

Treatment—Treatment is symptomatic It consists of bed rest sedation with doses of morphine sufficient to control pain and the exclusion of surgical operation for acute abdomen renal colic or arterial embolism

BIBLIOGRAPHY

BAER S AND FRANKEL, H Studies in acute myocardial infarction I The clinical picture and diagnosis Ann Int. Med 20 108 1944

——— II Laboratory procedures as diagnostic aids ibid. 20 115 1944

——— III Diagnos s and location of infarct by electrocardiog am Arch Int Med 3 786 1944

BECK C. Prin iples underlying operative approach to treatment of myocardial ischemia Ann. Surg 118 788 1943

BELLET S KERSCHBAUM A MEADE, R. H JR., AND SCHWARTZ, L. The effects of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation Am. J M Sc 201 40 1941

BOYER N H Premonitory symptoms of myocardial infarction New England J Med 22 6 8 1942

DAVIS N AND KLAINER M. J Studies in hypertensive heart disease I The incidence of coronary atherosclerosis in cases of essential hypertension Am Heart J 19 185 1940

——— II Role of hypertens on per se in the development of coronary scleros s ib d 19 193 1940

——— III Factors n production of angina pectoris ibid 19 198 1940

——— The concept of hypertensive heart disease New England J Med 224 6 9 1941

DE LA CHAPELLE, C. E The management of the acute ep sode in coronary oc clus on Bull New York Acad Med 19 201 1943

EDMONSON H A AND HOXIE H J Hypertension and cardiac rupture Am. Heart J 24 19 1942

ELEK S R AND KATZ, L. N Some cl nical uses of papaverine in heart disease J A M A 120 434 1942

ERNSTENE, A. C Coronary Heart Disease American Lecture Series (Spring field Ill Cha les C Thomas Publi her 1948)

FEIL H Premonitory pain in coronary thrombosis, Am. J M Sc 193 42 1937

——— A clinical appraisal of the Beck operation Ann Surg 118 807 1943

FENN C K Ang na pectori M Clin North Amer ca 28 16 1944

GILBERT N C. Treatment of coronary thrombosis M. Clin. North America 28 1 1944

HARRISON T R. Cl n cal aspects of pain in the chest I Angina pectoris Am J M Sc 20 561 1934

HELLERSTEIN H K AND MARTIN J W Incidence of thromboembolic le ons a companying myocard al infarction Am. Heart J 33 443 1947

HORN H AND FINKELSTEIN L F Atheroscleros s of coronary arteries and the mechan sm of occlus on Am Heart J 19 655 1940

KATZ L N COLDMAN A LANGENDORF R. KAPLAN L G AND KILLIAN S T The d agnost c value of the electrocard ogram based on an analysis of 149 autopsy ases Am. Heart J 24 627 1942

KOUNTZ, W H AND SMITH J R. The flow of blood in the coronary arter es in pathological hearts J Clin Investigation 17 147 1938

The patient is usually a male who has hypertension The onset with tearing or crushing chest pain, simulates myocardial infarction The pain of partial rupture is commonly severe and not readily relieved by morphine It differs from the pain of infarction in that it does not commonly radiate to the arms, it radiates to the interscapular region and may travel down the back from the neck to the legs

The symptoms and signs are (1) those of extravasation (fever and leukocytosis) and (2) locally those caused by interference with circulation The local signs vary as extravasation progresses toward or away from the heart and from its more usual point of origin in the ascending aorta A cardiad direction leads to encroachment on the aortic ring so that sudden onset of aortic insufficiency with pain in the back or legs clearly indicates dissection A coronary artery may be occluded Such an extravasation is usually completed by rupture into the pericardium with cardiac tamponade or into the mediastinum or pleura

Distally directed extravasation causes signs which vary with the arteries whose aortic mouths are compressed by the hematoma Carotid or innominate occlusion causes cerebral symptoms innominate or subclavian occlusion marked asymmetry of arterial pressure The more common signs arise from obstruction of a renal artery with renal infarction and of arteries to the lumbar cord with pain and partial or complete paraplegia

In contrast to myocardial infarction the height of the blood pressure is maintained or sometimes increased and the heart while enlarged shows no weakness of sounds or characteristic electrocardiographic change The diagnosis may be confirmed by radiographic demonstration of suggestive distortions of the aorta or one of its branches

The prognosis at present highly unfavorable may lengthen into years as has that of myocardial infarction Minor so called silent dissections are thought to occur and even a clearcut syndrome may be followed by recovery

Still most of the common methods of treatment have long been established It is by applying these that the physician does much to alleviate the patient s distress and hold the condition in check dur ing months and even years

Congestive heart failure often develops slowly during months and years of myocardial strain and cardiac hypertrophy On the other hand as we have seen it may be suddenly precipitated by myocardial infarction in which case it adds to a gloomy prognosis Or it may slowly appear in a patient who is already the victim of angina pectoris or coronary insufficiency Sometimes it is brusquely set off by the onset of auricular fibrillation when it can be as dra matically relieved by quinidine (p 194) In a few patients as a matter more of academic than clinical interest, the debate arises as to whether congestive failure is to be attributed to hypertension or to rheumatic heart disease when both conditions are present

MECHANISM

The observations of Stead McMichael and others who base their conclusions on determinations of cardiac output by the cathe terization method of Cournand have greatly clarified some of the mechanisms of this condition Earlier observations (Schroeder Schemm Merrill) established the position of the sodium ion in pathogenesis and treatment

The ultimate causes of congestive heart failure of slow onset are cardiac hypertrophy and overwork Between them there results an encroachment on the cardiac reserve until it becomes inadequate to the patient s needs Hypertrophy does this by increasing the size of muscle fibers beyond the level of efficient nutrition And the strain and overwork of maintaining a high arterial tension further narrow the gap between what the heart can do and what it must do to maintain a normal circulation As the point of failure is reached even the chemical constitution of the myocardium begins to change There is for example a decrease in the creatine which thus becomes

LEVINE S A AND ROSENBAUM F F Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction I Immediate prognosis Arch Int Med 69 913 1941
——— II Ultimate prognosis ibid 68 1215 1941
LEVY R L The management of the patient who has recovered from acute coronary occlusion Bull New York Acad Med 19 273 1943
MASTER A M JAFFE H L DACK S AND LEWIS N Course of blood pressure during and after coronary occlusion Am Heart J 26 92 1943
——— DACK S AND JAFFE H L Premonitory symptoms of acute coronary occlusion A study of 100 cases Ann Int Med 14 1155 1940
——— STRICKER J GRISHMAN A AND DACK S Effect of undernutrition on cardiac output and cardiac work in overweight subjects Arch Int Med 69 1010 1942
OPDYKE A F AND SELKURT E M A study of alleged intercoronary reflexes following coronary occlusion Am Heart J 36 73 1948
PETERSEN J C Some factors in the causation of intimal hemorrhages and in the precipitation of coronary thrombi Canad M A J 44 114 1941
PINES I SANABRIA A AND HERNANDEZ ARRIENS R T Mercurial diuretics Addition of magnesium sulfate to prevent toxic effects of their intravenous administration Brit Heart J 6 197 1944
PRESSLER W Myocardial infarction indicated by angina pectoris of effort or by brief attacks of angina of rest with brief remarks on premonitory pain Am Heart J 28 81 1944
RISEMAN J E F The treatment of angina pectoris New England J Med 229 670 1943
SHAFFER C F Electrocardiographic study of lateral infarction proved at autopsy Am Heart J 28 39 1944
THOMSON H E AND FEIL H Infarction of the lateral wall of the left ventricle pathologic and electrocardiographic study Am J M Sc 207 508 1944
WHITE J C AND SMITHWICK R H Autonomic Nervous System Anatomy Physiology and Surgical Application (2d ed New York The Macmillan Company 1941)
WOODS R M AND BARNES A R Factors influencing immediate mortality after acute coronary occlusion Am Heart J 24 4 1942
WRIGHT I S *et al* Report of the Committee for the Evaluation of Anticoagulants in Treatment of Coronary Thrombosis with Myocardial Infarction Am Heart J 36 801 1948

III CONGESTIVE HEART FAILURE

Because congestive cardiac failure is that manifestation of hypertensive heart disease which most often causes disability and death it is the most important to the clinician Paradoxically this common and significant condition is in many quarters the least well understood and in a few the least well treated Of course the basic mechanisms of congestive failure have not been clarified to everyone's satisfaction although much has been accomplished in recent years

definition the absolute level of cardiac output may not be low It may even be abnormally high, as in thyrotoxicosis or in arteriovenous fistula. But, for any given level of metabolic need, it is lower than it was when the patient was well and lower than it will be when his heart is fully compensated again Actually in congestive heart failure associated with hypertensive heart disease the level of cardiac output is usually somewhat below the normal average

More particularly when failure is of sudden onset so that there is no time for the accumulation of peripheral edema and when as in hypertensive disease it is the left ventricle which is under the greater strain there may be a temporary disparity of output between the ventricles so that filling pressure must rise on the left before it again puts out as much as the right side has discharged into the lungs This increase of left auricular pressure results in venous congestion in the lungs Pulmonary congestion and edema set off reflex impulses which result in dyspnea and discomfort Since nervous stimuli are among the principal determinants of the levels of both cardiac output and arterial tension it is not surprising that a vicious cycle of pulmonary congestion—dyspnea increased left ventricular strain and relatively decreased cardiac output—is set in train This same mechanism probably obtains in congestive failure of slow onset although in such cases it has other concomitants

'Whenever as Leiter says the circulation is exposed to stress whether from sudden large hemorrhages loss of circulating plasma into a traumatized area or other types of shock or dehydration all associated with an inadequate cardiac output a redistribution of available blood flow occurs whereby the more vital organs are supplied at the expense of blood flow to skin muscles gastrointestinal tract and kidneys In the kidneys as we and others have shown the onset of shock to say nothing of shock itself leads to a profound decrease of renal blood flow and glomerular filtration Some decrease of renal blood flow and glomerular filtration beyond normal levels or the levels the patient can reach on adequate treatment is

unavailable to form creatinephosphate for contraction energy Finally failure itself provokes still more hypertrophy so that heart failure runs in a vicious cycle

The overlapping of the need for work and the capacity to perform occurs first during effort, especially during effort associated with emotional strain This is because nervous even more than hemodynamic factors determine the level of cardiac output and because output is especially increased by anxiety The patient says that at such times he loses his breath Later the overlap appears during ordinary effort or during minor emotional strains, and last it is present at rest and even during sleep In all these situations failure is predisposed to by even minor infections, presumably because the catabolic impulse of infection or trauma aids in depleting the chemical structure of the myocardium

Allbutt chivalrously suggested that this process be called cardiac defeat and not cardiac failure He thought that the heart in hypertension is honorably overcome by superior force and he was unwilling to grant the implication that it had shamefully surrendered its task One merit in this phrasing is the sense it gives the physician of his participating as an ally rather than as a mediator of terms He should recognize that had he been able to find means of maintaining arterial pressure at more nearly normal levels throughout the preceding years the possibility of cardiac defeat would have been staved off or even avoided Alternatively, had he been able to increase the number and size of the myocardial capillaries and perhaps to change the laws of physical diffusion failure might have been postponed But lacking these beggars horses he must deal with the situation as he finds it and as an ally

In so doing a concept of the mechanism at fault is very helpful The fundamental fact as phrased by Leiter is that In congestive failure the output of the heart is inadequate for the body s requirements even at rest and certainly during exercise or any other condition that increases metabolism and the load on the heart By this

The increase in venous pressure and the preceding increase in blood volume have still other effects One is an increase first in return flow and then in both flow and pressure of return of blood to the right ventricle Unable perhaps to transmit this excessive volume into an engorged pulmonary circuit the right ventricle in turn begins to fail and edema tends to increase still more

Thus in considering the mechanism of congestive cardiac failure we deal with an interlocking gear train arranged in series in which the prime movers seem to be the heart, more particularly the left ventricle on one hand and on the other the ability of the kidneys to maintain a normal sodium balance

To summarize the mechanisms underlying the phenomena of congestive cardiac failure are (1) absolute or relative decrease in cardiac output and (2) vasoconstriction in *kidneys skin* and *splanchnic circulation* As a result of vasoconstriction there is decreased excretion of salt the content of which in the body is no longer strictly regulatable according *to need*. From this accumulation of salt, hypervolemia and peripheral edema result with increased venous pressure both pulmonary and peripheral Meanwhile the fact that the left ventricle *is the one* predominantly under stress tends to increase pressure in the pulmonary circuit so that dyspnea is a presenting symptom And since renal blood flow and filtration disproportionately *decrease during* the day another clinical result is nocturia in the absence of renal excretory failure This sequence of events presupposes initial left ventricular failure which in contrast with former explanations is followed by sodium retention before the function of the *right heart* is altered.

EVIDENCES OF CONGESTIVE FAILURE

The imminence or presence of failure is usually brought to the patient's notice by the onset of nocturia and dyspnea or edema The persistence or change of this evidence is also the major principle of success or failure of treatment.

usually but not invariably, present in congestive heart failure A reduction in the rate of glomerular filtration decreases the mass of sodium chloride presented to the tubules for reabsorption or excretion Normally, the tubules return to the blood some 98 or 99 per cent of the sodium presented to them in the glomerular filtrate If the volume of filtration is reduced and the rate and limits of reabsorption remain about the same, there will be an increase in the proportion of sodium reabsorbed so that, say 98 5 or 99 5 per cent is filtered The difference is not large when phrased in this way and it is a very difficult one to prove by semidirect measurement Measurements with radioactive sodium have most accurately established the decreased sodium excretion in congestive failure When we recall that the mass of sodium chloride filtered each day is about 2½ lb a difference of one half of 1 per cent becomes important The difference equals 6–8 Gm or about 1 L when diluted in extracellular fluid Consequently the deficit in sodium excretion imposed by decreased glomerular filtration in the example equals a gain in weight as edema of 2 lb or 1 kg per day The water retained is distributed in the interstitial fluid and plasma Ultimately the tendency to hydremia of the plasma is countered by a gain in red cell mass so that total blood plasma and red cell volumes are increased more or less in parallel with the increased interstitial fluid

The result of this plethora is a rise in venous pressure and the accumulation of edema in the liver intestinal tract and dependent areas of the body Since exercise reduces renal blood flow and glomerular filtration even in normal people exercise in people with impending congestive failure further accelerates the retention of sodium and water The exercise is carried on by day whereas during rest renal blood and filtration rise with the result that salt and water are lost at night Consequently one of the first evidences of congestive cardiac failure is nocturia Especially in patients with hypertension it is important to distinguish cardiogenic nocturia from the hyposthenuric nocturia of advanced renal disease

patient may be awakened slightly during the hyperpneic phase and doze again as respiratory excursions are lessened and slowed This form is not usually associated with acute pulmonary congestion but is more characteristic of advanced congestive failure with chronic congestion. It is more common and less ominous in older people than in those under 50

Continuous dyspnea occurs in advanced congestive failure It causes great disability and discomfort. When neither the relief of edema nor the administration of digitalis abolishes it, the prognosis is grave

Edema—The edema of congestive failure is almost entirely due to retention of sodium. The retention is not as has been thought, an avidity of tissues or a specific renal defect or even a result of venous congestion with increased back pressure and excess formation of interstitial fluid While at times cardiac edema is contributed to by associated hypoproteinemia this is never a principal and determining factor Rather the real cause is renal *retention* of sodium The principal mechanism by which the kidney tends to retain sodium in heart failure is a decrease in the rate of glomerular filtration a defect which is exaggerated during exercise That there may be associated with this more or less mechanical retention consequent on deficient supply with continued renal tubular demand a factor of increased tubular reabsorption of sodium is suggested by certain observers Such an increase beyond the normal in the fraction of the filtered sodium reabsorbed might be attributable to increased adrenocortical (mineralocorticoid) activity But as yet an adrenal participation has not been demonstrated beyond question while a renal deficit is present in nearly every case

The edema may be pulmonary only manifest as dyspnea and as fine rales or perhaps extending to the point where there is dulness and even hydrothorax These various stages and kinds of pulmonary edema are for the most part due to the combination of left ventricular failure and an increase in total blood volume Normally a

Dyspnea—The dyspnea of congestive heart failure is probably initiated by pulmonary congestion on a high filling pressure of the left ventricle It is not, at least in its early and even in some of its most distressing phases due wholly to replacement of pulmonary alveolar surface by edema Rather, edema of the alveolar spaces sets in train reflexes which elicit dyspnea

Dyspnea may be classified as (1) exertional, in which the severity and conditions of exertion should be noted, (2) resting or (3) continuous

Dyspnea at rest is usually nocturnal and may appear before the patient has gone to sleep in the form of orthopnea and trepopnea or of evening dyspnea The association of dyspnea with the recumbent posture is apparently due to the increase in blood volume which occurs on lying down To this factor are added the decreased diaphragmatic excursion which follows recumbency and in some patients, an increase in auricular pressure Orthopnea is dyspnea provoked by recumbency and relieved by the patient s assuming a semierect position, trepopnea (Gr *trepo,* I turn) is dyspnea provoked more by lying on one side, commonly the left, than on the other Evening dyspnea is dyspnea elicited after the day s fatigues by conditions which would not cause dyspnea in the morning Dyspnea which appears after the patient has gone to sleep and wakes him or disturbs his slumber is usually paroxysmal and takes the form of cardiac asthma The attack is precipitated by anything which may transiently throw strain on the slowed circulation of sleep such as a full meal a warm room a nightmare or a fit of coughing It may last for some minutes and in its mild forms is relieved by sitting up and coughing once or twice to aid in the discharge of transient pulmonary congestion In its severe forms it progresses to pulmonary edema with manifest acute failure of the left ventricle mild severe or even fatal The other form of sleep disturbing dyspnea is periodic breathing of the Cheyne Stokes type In deep sleep the respiration alternately is depressed and stimulated in cycles the

lem In such cases the Gatch bed or the so-called cardiac chair bed is superior to the ordinary variety because the patient can sit up even while asleep Side railings should not be forgotten Often patients prefer to sit on the side of the bed for short periods Usually they are the best judges of what posture gives the greatest comfort and correspondingly optimal conditions for the circulation

Except during the acute phases of failure strict rest need not be enjoined. Many physicians believe that strict bed rest has been over done We think our patients have done better since they have been allowed more latitude and especially since we have tried to keep the muscles in better tone by means of bed exercise and gentle physical therapy The fact that exercise aids in the return of lymph to the circulation indicates that this view has a physiologic basis

No two physicians are likely to agree on the time a patient should be allowed to desert the bed Actually there is seldom a sharp dividing line The scales and the patient s response are probably the two simplest criteria.

Once the patient is up experience will usually teach him what he can and cannot do It is perhaps well for him to experiment a little with the effect of standing and on occasion even of salt on the occurrence of edema Such experiments may have impressive pedagogic value Hydrotherapy and massage may be helpful but Turkish baths and strenuous massage should be clearly interdicted.

Diet —Diet is important in heart failure because it influences the work of the heart and the amount of sodium provided the kidneys for retention

The volume and type of food ingested may have immediate disturbing effects A hearty meal has long been recognized as a precipitating cause of sudden death in cardiac patients Many patients become more dyspneic or have more cardiac distress after meals especially when eating is associated with aerophagia or the foods are gas forming This is partly because cardiac output arterial pressure cardiac work and the heart s requirement for oxygen are

considerable fraction of the total blood volume is at any moment passing through the lungs and an increase in the total volume increases this fraction and so augments the congestion due to left ventricular deficit

Or the edema may be largely peripheral either latent or manifest Since edema in the last analysis is an abnormal increase in the ratio of extracellular fluid to cellular mass there is necessarily a latent phase in which pitting edema is not present and the changes in body fluid can perhaps be most readily measured by following body weight from day to day Actually latent edema may represent an abnormal accumulation of as much as 10 L of body fluid During this phase and usually before pitting edema appears in the ankles or shins there will have been nocturia the liver will have become congested tender and large Thus the course of cardiac edema is perhaps best followed by repeatedly measuring the body weight and noting also the position and tenderness of the left edge of the liver in the right midclavicular line

TREATMENT

Treatment of the failing heart depends on the intelligent use of five important agents rest diet water and salt digitalis and diuretics As in many current treatments their separate and often combined use has developed over several decades Modern treatment is the refined culmination and co ordination of many years of careful clinical research

Just as the blood pressure and fluid intake and output should be taken daily and charted so should the weight of the patient It is an extremely practical and accurate guide to treatment In this condition the bathroom scales are of more value than the clinical thermometer

Rest and exercise —The amount of rest and exercise depends on the degree of congestive failure If very mild complete bed rest may not be necessary If severe the *patients themselves settle the prob*

lem In such cases the Gatch bed or the so-called cardiac chair bed is superior to the ordinary variety because the patient can sit up even while asleep Side railings should not be forgotten Often patients prefer to sit on the side of the bed for short periods Usually they are the best judges of what posture gives the greatest comfort and correspondingly optimal conditions for the circulation

Except during the acute phases of failure strict rest need not be enjoined Many physicians believe that strict bed rest has been over done We think our patients have done better since they have been allowed more latitude and especially since we have tried to keep the muscles in better tone by means of bed exercise and gentle physical therapy The fact that exercise aids in the return of lymph to the circulation indicates that this view has a physiologic basis

No two physicians are likely to agree on the time a patient should be allowed to desert the bed Actually there is seldom a sharp dividing line The scales and the patient s response are probably the two simplest criteria

Once the patient is up experience will usually teach him what he can and cannot do It is perhaps well for him to experiment a little with the effect of standing and on occasion even of salt on the occurrence of edema Such experiments may have impressive pedagogic value Hydrotherapy and massage may be helpful but Turkish baths and strenuous massage should be clearly interdicted

Diet —Diet is important in heart failure because it influences the work of the heart and the amount of sodium provided the kidneys for retention

The volume and type of food ingested may have immediate disturbing effects A hearty meal has long been recognized as a precipitating cause of sudden death in cardiac patients Many patients become more dyspneic or have more cardiac distress after meals especially when eating is associated with aerophagia or the foods are gas-forming This is partly because cardiac output arterial pressure cardiac work and the heart s requirement for oxygen are

increased during digestion, particularly of protein food Some of the distress arises because a full stomach elevates the diaphragm and displaces the heart transversely into a position where it is believed to work less efficiently at the same time reducing vital capacity and compressing alveoli

During the initial phase of treatment when the patient is usually too sick to take more than very simple food the Karrell diet is satisfactory and practical It consists of 800 cc of milk given in 200 cc portions at convenient intervals during the 24 hours Milk is low in salt calories and protein, is simple to take and fulfils the need of the very sick patient But the ration is inadequate and annoying over any long period, so that it is seldom continued for more than a week It also has the disadvantage of very low fluid content while salt excretion is aided and discomfort decreased by moderate water diuresis Thus, 800 cc of milk with 2 L or more of water during the 24 hours is a more satisfactory ration If the patient becomes hungry boiled rice milk and sugar are given Reconstituted salt poor milk such as lonalac® may also be advantageous

When the time comes to supply solid food the need remains for a diet with small bulk, little sodium few calories and no more than a moderate protein content Master and his co workers called attention to the reduction of oxygen consumption and cardiac work caused in two to four weeks by an 800 calorie diet consisting of 80 Gm carbohydrate 50 Gm protein and 30 Gm fat Since the protein ration is adequate edema will not be aggravated by nutritional hypoproteinemia Many of their patients remained ambulatory for three to 12 months on diets of 800–1 200 calories Ketosis does not develop Loss of weight which is especially desirable in the obese, is at first rapid then tends toward a plateau The low caloric value (800) of the initial diet may lead to weakness and fatigability which in the experience of both Master and Fishberg are usually transitory and may be alleviated by reserving portions for between meal collations Should these symptoms persist the caloric

value of the diet can be increased to 1200 or 1500 calories

The purpose of treatment is to limit the energy value of the diet to a point where cardiac work is reduced to a level in keeping with the heart s capacity for work while maintaining somewhat less than ideal body weight and a feeling of relative well being

TABLE 9—CARDIAC DIET (FISHBERG)

Breakfast
- Fruit
- Ce eal
- 1 egg
- 6 oz. of weak tea or coffee

Midmorning
- 6 oz of milk with cracker

Dinner
- Boiled or broiled, tender meat chicken or fish
- Vegetables
- 1 slice thinly buttered bread or toast
- Gelatin dessert or stewed fru t
- 6 oz. of weak coffee or tea

Midafternoon
- 6 oz. of milk with cracker

Supper
- Fish, chicken egg or cottage cheese
- Salad with mineral oil dressing o vegetables
- 1 slice thinly buttered bread or toast
- Light pudding or custard
- 6 oz. of weak coffee or tea

Before retiring
- 6 oz. of hot milk or malted milk

The results of this diet in hypertensive arteriosclerotic heart dis ease are often dramatic especially when the patient is obese Car diac discomfort and dyspnea are reduced and even the tendency to fluid retention is diminished in some instances the arterial pressure is also favorably affected.

Frequent meals advised with these diets make for small meals

which in the cardiac patient are altogether desirable A schedule of *breakfast, midmorning noon, midafternoon and early evening* collations fulfils this purpose Neither food nor fluid is taken during the late evening Cold and carbonated liquids are at all times avoided It is important that the diet be well balanced Fishberg recommends a practical diet (Table 9), emphasizing that the choice of food depends on individual likes dislikes and idiosyncrasies

Salt and water—The third major aspect is control of sodium intake at minimal practical levels This is necessary because a high or normal sodium intake maintains or increases edema while a low one causes loss of water The maintenance of a low sodium intake is necessary not only in patients with evident edema but in those with the latent variety

Obviously the control of salt content of the diet depends on the facilities available for its preparation Some clinicians feel that *salt should be rigidly restricted so that urinary excretion of sodium* (in terms of sodium chloride) is less than 1 Gm daily Such control requires careful selection and supervision of the foods Until the advent of salt free milk powder (Lonalac*) such restriction has been possible only in a hospital (see p 358) Diets containing as little as 200 mg of sodium per day but adequate in protein and calories can now be prepared in the home Others believe that an intake of sodium which causes excretion of 2–3 Gm of sodium chloride is low enough This level is readily attainable in the home It is well to point out that whether in hospital or in the home many patients never receive a sodium poor diet This is usually due to lack of understanding by the patient or his attendants Some are under the impression that bacon is salt poor and others hasten to relieve gastric distress with sodium bicarbonate For such reasons quantitative determination of the urinary sodium or *chloride excretion* in a 24 hour specimen should be done occasionally after the salt poor regime has been established for three or four days and repeated at weekly or monthly intervals

Custom has sanctioned the restriction of fluids in treatment of cardiac edema But fluid restriction does not initiate diuresis indeed it depresses urinary output Furthermore about 1 cc of urine must be excreted per minute for maximal excretion of salt Urine volumes below this figure tend to lessen its excretion

Since water is rarely retained in the body unless there is sufficient salt to make physiologic saline solution salt is necessary for the formation of edema. Once sodium intake has been cut to 0 5 Gm daily or less there seems no reason for restricting water Usually 1 5–2 L daily is adequate Schemm has shown that the relief of edema is sometimes hastened by giving larger quantities but Wood showed that excretion of salt is often reduced when water intake exceeds 3 L hence there seems no reason for exceeding this amount Advanced renal insufficiency due to renal parenchymal injury is an indication for strict control of fluid and electrolyte intake at optimal levels neither too small nor too large Such patients like those too persistently plied with mercurials pass into oligemia azotemia and oliguria because of an excessive drain on the electrolytes

Digitalization—Congestive failure resulting from hypertension is always to be treated with digitalis Always is seldom true in medicine but we know of no exception to this dictum in the management of the hypertensive Thus patients with congestive failure with or without auricular fibrillation with slow or fast rate with or without heart block should receive it. Normal rhythm and rate even if slow are not contraindications The height of the arterial pressure plays no part in the decision whether or not to give digitalis *The chief and almost sole criterion is the presence of congestive heart failure*

The choice of digitalis preparation has been the subject of extensive studies There can be little doubt of the desirability of an inexpensive orally acting pure glucoside which would have all of the favorable attributes of the mixed glucosides from the whole digitalis leaf None of the many preparations that have appeared on

the market has displaced the highly reliable dried powdered leaf of digitalis

Rarely in the course of hypertension is digitalization so urgent that the drug cannot be given by mouth If the situation is very urgent ouabain is given (0 3–0 5 mg) intravenously in 10 cc of saline over 5 or 10 minutes Its full effect is apparent in about two hours It is inactive orally Results with cedilanid® (lanatoside C), a pure glucoside from Digitalis lanata used both orally and intravenously, seem good It can cause intoxication similar to that from excess Digitalis purpurea but this is said to pass off more quickly It is sometimes tolerated when other digitalis bodies are not

Before any cardiac glucoside is given it is essential to ascertain whether the patient has already received one of them This is especially important if a glucoside is to be administered intravenously If an unknown amount has recently been given, attempts to digitalize by the intravenous method are dangerous

DOSAGE Eggleston s observation that 0 1 Gm of dried digitalis leaf per 10 lb of body weight produced satisfactory digitalization in most patients is the basis for most rules of dosage of digitalis leaf Clinical experience has shown that this formula is approximately correct Its strict application depends on knowledge of the normal weight before edema occurred a datum sometimes not easily available and therefore estimated from the patient s build Most adults given 1 5 Gm of dried powdered digitalis leaf by mouth during a 24 hour period become fully digitalized The initial dose is 0 5 Gm (7½ gr) and the remainder is administered in divided doses within 24 hours

Digitoxin long favorably known in Europe has been enthusiastically received in America Gold whose experience is large, says For the routine treatment of cardiac failure the oral is the route of choice digitoxin (Digitaline Nativelle) is the glycoside of choice and digitalization in a single dose the method of choice

Gold and his group estimated the average initial digitalizing

dose as 1.2 mg orally or intravenously and daily maintenance dose as 0.2 (sometimes 0.1) mg DeGraff Batterman and Rose found the average therapeutic dose to be larger (0.9–4.8 mg mean 2.2 mg given in divided doses at six hour intervals 1.6–4.5 mg mean 2.7 mg in a single dose scheme) Signs of toxicity appeared at mean dosages of 3.8–4.6 mg They have emphasized the value of multiple dose digitalization and concluded that digitoxin has no advantage over digitalis leaf for routine treatment of these patients

Satisfactory digitalization is shown when rate rhythm and in fibrillation pulse deficit are restored toward normal when symptoms abate and diuresis begins Reduction in rate ordinarily is associated with improvement but is by no means an essential accompaniment. If electrocardiograms are being made frequently progressive flattening and finally inversion of the T waves in the standard leads may be noted Commonly but not invariably the T wave changes appear at dosage levels well below those of maximal therapeutic effectiveness The maintenance dose of digitalis leaf varies from patient to patient but usually is 0.1–0.2 Gm (1½–3 gr) a day A few patients require 0.3 Gm (4½ gr) but these should be watched carefully for signs of toxicity

In our experience the cardinal sin in the use of digitalis is giving too little When there has been an adequate indication for its use sufficient glucoside or leaf should be given to cause full digitalization during the first 24–36 hours followed then by a clinical titration to ascertain the proper maintenance dose

SIGNS AND SYMPTOMS OF GLUCOSIDE TOXICITY These are protean One is probably no more important than another and they occur in a wide variety of combinations For this reason constant watchfulness is necessary especially while the maintenance dose is being ascertained

The most common signs of toxicity are loss of appetite nausea and vomiting headache drowsiness and confusion coupled rhythm and partial auriculoventricular block There are others—diarrhea

the market has displaced the highly reliable dried powdered leaf of digitalis

Rarely in the course of hypertension is digitalization so urgent that the drug cannot be given by mouth If the situation is very urgent, ouabain is given (0 3–0 5 mg) intravenously in 10 cc of saline over 5 or 10 minutes Its full effect is apparent in about two hours It is inactive orally Results with cedilanid* (lanatoside C), a pure glucoside from Digitalis lanata, used both orally and intravenously seem good It can cause intoxication similar to that from excess Digitalis purpurea but this is said to pass off more quickly It is sometimes tolerated when other digitalis bodies are not

Before any cardiac glucoside is given it is essential to ascertain whether the patient has already received one of them This is especially important if a glucoside is to be administered intravenously If an unknown amount has recently been given attempts to digitalize by the intravenous method are dangerous

DOSAGE Eggleston s observation that 0 1 Gm of dried digitalis leaf per 10 lb of body weight produced satisfactory digitalization in most patients is the basis for most rules of dosage of digitalis leaf Clinical experience has shown that this formula is approximately correct Its strict application depends on knowledge of the normal weight before edema occurred a datum sometimes not easily available and therefore estimated from the patient s build Most adults given 1 5 Gm of dried powdered digitalis leaf by mouth during a 24 hour period become fully digitalized The initial dose is 0 5 Gm (7½ gr) and the remainder is administered in divided doses within 24 hours

Digitoxin long favorably known in Europe has been enthusiastically received in America Gold whose experience is large, says For the routine treatment of cardiac failure the oral is the route of choice, digitoxin (Digitaline Nativelle) is the glycoside of choice and digitalization in a single dose the method of choice

Gold and his group estimated the average initial digitalizing

especially when venous pressure was much elevated and when as much as 600–800 cc of blood was removed

If bleeding or bloodless phlebotomy is successful dyspnea due to pulmonary congestion is quickly relieved venous pressure falls and the liver decreases in size Fishberg recommends bleeding not only when there is systemic venous engorgement but also in isolated left heart failure with pulmonary but no systemic venous engorgement. The effect is to lessen the pulmonary engorgement as demonstrated radiographically by clearing of previously clouded lung fields We believe it likely that this latter situation where there is temporary cardiac disability without a marked increase in blood volume is that in which the bloodless method is specifically indicated

Other drugs—Patients who are acutely ill from heart failure may require morphine to relieve respiratory distress and their anxiety Some combine it with atropine Perhaps atropine aids in drying up bronchial secretions and by providing a freer air passage better lung movement and lymph drainage hastens the resolution of pulmonary edema Eggleston thinks 1 3 mg (1/50 gr) of atropine is the minimal dose which is of any value and our experience coincides with his Its dosage should be gaged quite independently of the amount of morphine given

Pulmonary edema and particularly Cheyne Stokes *respiration* may at times be dramatically controlled by intravenous *administration* of aminophylline Eggleston recommends a dose of 0 5 Gm ($7\frac{1}{2}$ gr) taken up in 20 cc of saline and injected *slowly* during 10 or 20 minutes The action is prompt if it is to be effective at all often it gives a temporary respite while other measures such as bleeding bloodless phlebotomy oxygen inhalation and digitalization are being instituted

Diuretics—In the past few years the use of diuretics in treatment of congestive failure has greatly increased Not many years ago they were scarcely used at all and even this use was frowned

oliguria visual disturbances urticarial or scarlatiniform rash—but they are not common

The problem with each patient is to decide how much digitalis to administer to obtain the desirable maximum effects and to recognize these once they have fully developed while avoiding undesirable toxic manifestations and to recognize these when they appear Digitalis is a drug with potentialities for good or for evil It should not be used timidly nor yet with a free and uncontrolled hand

Bleeding and bloodless phlebotomy —Much difference of opinion exists regarding the value of bleeding in chronic congestive failure Some have abandoned the practice and others urge its more frequent use We have used it only as an incidental procedure Bleeding in the absence of polycythemia, must be considered a temporary expedient for the relief of acute left ventricular failure and intense pulmonary engorgement During episodes of acute congestive failure when blood volume venous pressure and erythrocyte count are increased the removal of 600 cc of blood is a logical method of relieving temporarily the load on the heart

The bloodless method may be preferable This consists in application of tourniquets or inflated blood pressure cuffs to the four extremities as close to the trunk as possible sufficient compression being used to obstruct all the veins Usually this is about 80–100 mm Hg in the legs and half of this in the arms The tourniquets or cuffs are released serially every 10 minutes after a period of 20–30 minutes and reapplied if need be The method temporarily traps more blood than blood letting Care must therefore be taken to avoid oligemic collapse Some careful observers believe blood letting still the procedure of choice in preventing early relapses into acute congestive failure Others vigorously disagree

Arterial pressure usually does not fall significantly after bleeding nor does the pulse rate change However venous pressure consistently falls and may remain at lower levels for several hours

It is doubtful that the additional trouble is always worth the effort or the risk of acidosis In the unusual patient when diuresis is in sufficient the addition of ammonium chloride may be tried

Diuretics used in congestive failure certainly make the patient more comfortable and may prolong life appreciably Peripheral edema often is prevented, and the severity of dyspnea and other symptoms due to pulmonary congestion are lessened Lessening of edema decreases plasma volume and so benefits the heart by di minishing its load

There is some disagreement regarding contraindications for use of mercurials Renal irritation shown by increased numbers of red cells proteinuria or cylindruria, does not interdict their use since most patients with severe heart failure show such urinary changes as the result of failure without having glomerulonephritis It has been general experience that when the edema is predominantly due to congestive failure mercurial diuretics may be used without fear of damaging the kidneys When severe renal damage has occurred as in advanced malignant hypertension they have little value and may be dangerous

Reactions to mercurial diuretics may be immediate minor or lethal or delayed. The former are usually characterized by dyspnea apprehension sweating substernal discomfort and increase in pulse and respiratory rates Cyanosis and collapse may occur Fatal reac tions seem to be due to ventricular fibrillation (p 195) The de layed reactions usually consist of asthmatic attacks with pulmonary edema Fever and a rash may follow There is no denying that mer curial diuretics have their dangers especially when given intra venously This is testified to by the number of reports of fatal reactions But their usefulness surely outweighs their dangers if the indications for their use are real

Oxygen inhalation—Weakness of the left ventricle causes the lungs to become engorged with blood and the increased pul monary capillary pressure so induced results in transudation The

upon in many quarters Perhaps the efficiency and decreased toxicity of the modern mercurial diuretics has changed all this

Instead of waiting, as in the past, until as much edema fluid as possible has been lost under the influence of digitalis, the tendency is to start diuretic therapy concurrently with digitalization Thus, 0 5 cc of mercuhydrin® is given intramuscularly the first day and the amount of fluid lost noted If 2–3 lb is lost a day, diuresis is satisfactory Too small a diuresis is countered by increasing the dose up to 2 cc daily

Mercurial xanthine diuretics except thiomerin,® should be given deep in muscle it makes no great difference which ones are chosen The buttocks are the usual site There is less chance of dangerous reaction when they are given this way rather than intravenously But even given intravenously, the danger is not great provided they are given slowly

Gold prefers to give diuretics daily, along with digitoxin and salt poor diet until all signs of edema have disappeared and the weight declines to a resistant level the dry weight Thereafter, continued use of diuretic fails to reduce weight Salt poor food is then added to the diet and the patient is allowed to be up and about If the dry weight is maintained the amount of diuretic is gradually decreased until a stabilized level is achieved in which the injections are made at longer and longer intervals Most observers believe that the mercurials should be used rather more sparingly and our own practice is to rely somewhat less on them than does Gold On the other hand much depends on the circumstances in which the treatment must be carried out If it is in the home for example where very low salt diets are difficult to maintain more reliance must be placed on diuretics But these are matters the physician himself will decide

The use of 2 Gm (30 gr) of ammonium chloride three times a day during three successive days in the week along with mercurials increases diuresis about 15 per cent in the average patient

of congestive failure have been ameliorated or have disappeared the oxygen concentration may be gradually lowered. Two days at a concentration of 40 per cent and three days at 35 per cent may give sufficient acclimatization to atmospheric air

Paroxysmal cardiac dyspnea (cardiac asthma)—The clinical pattern of this manifestation of left heart failure is familiar Treatment is prophylactic in the first instance and consists in the general treatment of congestive failure plus special attention to light meals and fluid restriction before going to bed and to the sleeping posture The attack may respond to sitting up or standing it may require morphine or intravenous aminophylline or, in those who are not digitalized ouabain Failure of these measures is an indication for phlebotomy bloodless or not and for use of oxygen

BIBLIOGRAPHY

BARACH A. L. Principles and Practices of Inhalation Therapy (Philadelphia J B Lippincott Company 1944)

DeGRAFF A. C. BATTERMAN R. C AND ROSE, O A. Digitoxin J A. M A. 138 475 1948

FISHBERG A Heart Failure (Philadelphia Lea & Febiger 1937)

FLAXMAN N Clinical value of digitalis in hypertensive heart failure I With a normal rate and a regular rhythm Am J M Sc. 203 741 1942

GOLD H. *et al* A system for the routine treatment of the failing heart Am J Med 5 665 194

HARRISON T R AND FINKS R M Glucose deficiency as a factor in the production of symptoms referable to the cardiovascular system Am Heart J 6 14 1943

LEVY R. L. Drugs in the treatment of heart disease Ann Int. Med 11 1916 1938

PETERS J P AND VAN SLYKE D D Quantitative Clinical Chemistry (Baltimore Williams & Wilkins Company 1931)

SCHEMM F R. A high fluid intake in the management of edema especially cardiac edema Ann Int Med 17 952 1942

SCHROEDER H A Studies on congestive heart failure I The importance of restriction of salt as compound to water Am Heart J 22 141 1941

WARREN J V AND STEAD E. A. Fluid dynamics in chronic congestive heart failure An interpretation of the mechanisms producing the edema increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure Arch Int. Med 73 138 1944

WEARN J T Morphological and functional alterations of the coronary circulation Harvey Lect 35 243 1940

WIGGERS C. J Basic hemodynamics and principles essential to interpretation of cardiovascular disorders Bull New York Acad. Med 18 3 1942

WOLFERTH C. C The diagnosis and treatment of paroxysmal cardiac dyspnea M Clin North America 22 1 35 19 8

volume of potential air space is thus decreased Measurement of vital capacity demonstrates this in patients with congestive failure The reduced velocity of the flow of blood impairment of diffusion of oxygen through the edematous alveolar membrane and inefficient distribution of air in the alveoli all tend to reduce the amount of oxygen available to be carried to the tissues Prolonged circulation time through the greater circulation also increases the amount of oxygen removed from the blood so called stagnant anoxia To compensate for all these difficulties the volume of breathing must be increased

Cardiac dyspnea is thus due to several stimuli among them the increased breathing requirement impaired elastic properties of the lung CO_2 retention and proprioceptive impulses Barach has indicated that hypoxia is one of the major factors by showing that shortness of breath may be relieved by a 48 hour residence in an oxygen room despite the fact that vital capacity is unchanged or lower than before treatment

The average patient with early congestive failure due to hypertension does not need oxygen therapy unless the failure is exceedingly acute Occasional patients with chronic failure may be greatly improved by residence in an oxygen tent for a week or more The treatment is however only adjuvant to the use of digitalis and other measures Possibly it makes the patient more comfortable and that alone may justify its use

Barach finds that the atmosphere provided the patient should be not less than 50 per cent oxygen concentration and better 60 or 70 per cent A large well ventilated oxygen tent with completely transparent Pliofilm or Plastocele canopy lessens the feeling of claustrophobia and because it reassures is comfortable

During the first three days of oxygen administration dyspnea restlessness and apprehension are usually much improved and following this diuresis may occur Residence in the tent for two or three weeks may be required When the signs and symptoms

of congestive failure have been ameliorated or have disappeared, the oxygen concentration may be gradually lowered Two days at a concentration of 40 per cent and three days at 35 per cent may give sufficient acclimatization to atmospheric air

Paroxysmal cardiac dyspnea (cardiac asthma)—The clinical pattern of this manifestation of left heart failure is familiar Treatment is prophylactic in the first instance and consists in the general treatment of congestive failure plus special attention to light meals and fluid restriction before going to bed and to the sleeping posture The attack may respond to sitting up or standing it may require morphine or intravenous aminophylline or in those who are not digitalized ouabain Failure of these measures is an indication for phlebotomy bloodless or not, and for use of oxygen

BIBLIOGRAPHY

BARACH, A L Principles and Practices of Inhalation Therapy (Philadelphia J B Lippincott Company 1944)
DEGRAFF A C BATTERMAN R C AND ROSE, O A Digitoxin J A M A 138 475 1948
FISHBERG A Heart Failure (Philadelphia Lea & Febiger 1937)
FLAXMAN N Clinical value of digitalis in hypertensive heart failure I With a normal rate and a regular rhythm Am J M Sc 203 741 1942
GOLD H *et al* A system for the routine treatment of the failing heart Am J Med 3 665 1947
HARRISON T R AND FINKS R M Glucose deficiency as a factor in the production of symptoms referable to the cardiovascular system Am Heart J 26 14 1943
LEVY R L Drugs in the treatment of heart disease Ann Int Med 11 1946 1938
PETERS J P AND VAN SLYKE D D Quantitative Clinical Chemistry (Baltimore Williams & Wilkins Company 1931)
SCHEMM F R A high fluid intake in the *management* of edema especially cardiac edema Ann Int Med 17 952 1942
SCHROEDER H A Studies on *congestive heart failure* I The importance of restriction of salt as compound to water Am Heart J 22 141 1941
WARREN J V AND STEAD F A Fluid dynamics *in* chronic congestive heart failure An interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure Arch Int Med 73 138 1944
WEAR J T Morphological and functional alterations of the coronary circulation Harvey Lect 35 243 1940
WIGGERS C J Basic hemodynamics and principles essential to interpretation of cardiovascular disorders Bull *New York* Acad Med 18 3 1942
WOLFERTH C C The diagnosis and treatment of paroxysmal cardiac dyspnea M Clin North America 22 1 35 1938

11 Effects of Arterial Hypertension on the Brain

THE CEREBRAL consequences of hypertension—hemorrhage, thrombosis hypertensive encephalopathy vertigo tinnitus and headache—are mediated through its effects on the cranial vessels The frequency of these complications suggests that these vessels are especially susceptible to the injuries which hypertension causes Kety and his associates have ingeniously demonstrated that the brain shares in equal measure the generalized increase in vascular tone They have shown that cerebral blood flow and oxygen consumption remain within normal limits in patients with greatly increased arterial pressures so that in the group studied, mean cerebral vascular resistance was nearly doubled The degree of increase in resistance could be roughly correlated with the grade of retinopathy

It is all too easy to find structural explanations for the frequency of apoplexy whether hemorrhagic or thrombotic Cerebral arteries differ from arteries elsewhere in that their muscular walls are thin and their adventitias very weak and the vessels themselves once they enter the brain are unsupported and lie free in the perivascular spaces The intima of the cerebral arteries is well developed and although the degree of its hyperplasia in mature life does not equal that of the coronary arteries still its internal elastic membrane is normally split and fragmented at about age 50

The cerebral vessels therefore follow just behind the coronary arteries and aorta in the frequency of atherosclerosis The thin media and adventitia are more readily penetrated by atheromatous necrosis than are those of other vessels The courses of the arteries particularly those around the base are short so that the points of atherosclerotic predilection at branches are many The branches themselves come directly from large trunks and therefore are exposed to high pressure The more vulnerable perforating vessels arise from the posterior communicating anterior or middle cerebral arteries near the circle of Willis They supply the thalamus striatum and choroid plexus sending branches deep into the white matter of the cerebral radiations Their distribution supplies the sites of predilection for hemorrhage and thrombosis These branches are especially thin walled and in the direct line of the pressure wave from the heart. One such branch the lenticulostriate was once called the artery of cerebral hemorrhage Actually their anatomy is so variable that no one artery can be incriminated Indeed in Scheinker's concept, the site of bleeding is venous and not arterial

Apart from rupture the fat laden intima of atherosclerosis predisposes to occlusion of arteries by thrombosis The sometimes severe effects of apparently minor cerebral occlusions have been explained on the basis that cerebral arteries are end arteries This is rarely true for anastomoses among capillaries are extraordinarily profuse particularly in gray matter It is partially true *in the* sense that major collaterals are much rarer than in the myocardium. The better explanation seems to lie in the great sensitiveness of nerve tissue to oxygen want

The reaction of cerebral tissue to obliteration of blood supply is usually characteristic It consists in slow localized disintegration of nerve tissue and its replacement by proliferating glia ranging from a central focus and imperceptibly merging into normal tissue The pattern resembles that which hypertension causes in the kidneys and the analogy with so-called interstitial nephritis is

stressed in the name interstitial encephalitis which Ricker has given the change Cerebral arterioles in hypertension show intimal hyaline degeneration The concomitant capillary degeneration is one of homogenization and thickening of endothelial walls and proliferation of endothelium adventitia and glia Together the changes in arterioles and capillaries account for diffuse foci of cerebral softening and of gliosis The extent of these changes does not correspond in degree to the concurrent renal vascular disease (Scheinker)

The general causation of the *minor* cerebral manifestations of hypertension—encephalopathy, vertigo dizziness and headache—is a medley of structural and functional change Since the cerebral arterial media is weak the vessels tend not to constrict when constriction elsewhere has greatly increased arterial pressure Instead they may tend to dilate or only hold their own Their control depends on tonic dilatation especially by blood CO of vessels with a strong intrinsic tone Vessels elsewhere tend to tonic constriction Thus intense cerebral vasoconstriction can result from a diminution rather than an excess of stimuli Conversely the need for greater blood supply is probably met by dilatation brought about by increased local supply of vasodilator substances

Obliterating angiospasm seems a plausible explanation for many minor clinical phenomena To the argument that the weak media of cerebral vessels cannot sustain such constriction in the face of high arterial tension may be opposed the fact that the retinal arteries whose structure is similar are frequently seen to do so Thus though demonstrated only under rather extreme experimental conditions cerebral angiospasm is something more than an armchair hypothesis Unfortunately it is also a rather easy recourse for those prone to pat explanations and one which may cover ominous organic changes (p 228)

Vertigo results from a wide variety of stimuli The labyrinth has nerve connections through the vestibular nuclei to cerebellum

cerebral cortex and especially the ocular muscles Thus vertigo may arise not only from labyrinthine stimulation by rotation of the body and hot or cold water impinging on the ear but from stimulation of the ocular muscles for example during the production of eye strain The immediate cause is excitation of the semicircular canals or their central connections

Headache also may be given a measure of structural explanation Many headaches seem to arise in dilation of cranial arteries This dilation in a disease characterized by constriction would be paradoxical were it not for the intrinsic weakness and paradoxical responses of the cerebral arteries and the sensitiveness of the extracranial arteries to the pain of stretching Thus an attractive generalization is that arterial hypertension predisposes to headache by causing passive dilation of some of these vessels

CEREBRAL HEMORRHAGE

Massive hemorrhage or thrombosis in the brain is usually called apoplexy Although it is common in hypertensives it also occurs without hypertension chiefly because of atheromatous degeneration Hemorrhage alone will be considered now and thrombosis later though their causes seem to be much the same

Investigators do not agree regarding the precise mechanism of hemorrhage in the brain Three explanations are considered likely (1) Hemorrhagic infarction vasospasm and arteriocapillary damage result in venous dilatation and stasis and if prolonged in diapedesis through the vein and necrosis of its wall the massive hemorrhage usually results from confluence of smaller ones (2) Arteriolosclerotic narrowing (hyaline degeneration) and closure produce an area of softening which deprives the vessels of some of their support This loss contributes to rupture of a larger atheromatous vessel by the high arterial pressure It has been pointed out however that the semifluid softening which surrounds the vessel is under roughly the same pressure as that of normal tissue It may

be that these areas of softened brain contain proteases which act on an injured vessel wall (3) Rupture of a media weakened by sclerotic deposits seems the likeliest explanation at least in very old persons

Most views concerning the pathogenesis of cerebral hemorrhage at ages below 60 stress the prime importance of hypertension Especially in young and middle aged patients it causes hypertrophy of the media with increase in the number of nuclear elements of the large and middle sized arteries Hyperplastic change affects the internal elastic lamina Hyalinization is found in all of the smaller branches, even the capillaries Thus there are indications that the changes in the cerebral vessels in hypertension differ from the usual changes in arteriosclerosis of other organs In particular have been mentioned the facts (1) that the intimal hyperplasia of arteriosclerosis is infrequent in hypertensive cerebral arteriolar disease and (2) that in hypertension, diffuse hyaline degeneration of the entire wall is the most striking feature seldom complicated by such secondary changes as necrosis of a hyperplastic intima, fatty degeneration and sclerotic plaques usual in atherosclerosis elsewhere There are other differences but the question of whether a different pathogenesis is involved remains to be settled

In patients with advanced essential hypertension hyaline degeneration is associated with scattered areas of softening in the parenchyma destruction of nerve tissue and replacement by masses of gitter cells circumscribed foci of glial scar formation perivascular hemorrhages and diffuse or localized edema Undoubtedly these tissue changes are secondary to the arteriolocapillary changes If the patient survives after cerebral hemorrhage the hemorrhagic area may be replaced by a cyst Large numbers of scavenger cells originating from the microglia take up the debris Small cysts thus formed may be obliterated by proliferation of the neuroglia when the larger ones remain they become sequestered by glial zones

Malignant hypertension causes chiefly from medial change re

duction of the lumen Necrosis or calcification of cerebral arteries or arterioles is rare Rather the lesions are similar to those found in patients with essential hypertension differing only in their advanced degree and severe nature

Thus the brains of patients with malignant hypertension are often seriously damaged Hemorrhage with rupture into the ventricles may be the cause of sudden death. A second variety of change consists of small irregularly distributed hemorrhages throughout the white matter of the cerebrum and cerebellum They are associated with small infarcts Again diffuse capillary hemorrhages may be the principal lesions

Thus cerebral hemorrhage varies all the way from small petechial bleeding to massive extravasation The signs and symptoms depend not only on the extent but on the place

Without entering into a penetrating discussion of the signs and symptoms that foreshadow hemorrhage it may be useful to point out those five that Taylor and Page have found particularly useful in distinguishing hypertensive patients who will suffer stroke from those who probably will *not*. If the patient has any four of the following signs and symptoms the chances are that he will have a stroke within the following two years

1 Severe occipital or nuchal headaches

2 Vertigo or syncope

3 Motor or sensory disturbances (tingling paresthesias transient paralysis etc)

4 Nosebleeds

5 Retinal hemorrhages which are usually small discrete and often numerous in the absence of papilledema or exudates

An addendum to the list was suggested by Monteiro of Rio de Janeiro who finds that the artery of the malleus becomes visible on the tympanum of patients prone to apoplexy We have no experience with this physical sign.

The symptoms of major intracerebral bleeding are too well

known to need repetition here Of the several apoplexy aphorisms offered by Adams and Cohen one succinctly applies Apoplexy which causes sudden onset of headache confusion then deep coma hemiplegia and bloody cerebrospinal fluid under increased pressure is usually due to spontaneous cerebral hemorrhage Compared to thrombosis, cerebral hemorrhage more often causes conjugate deviation unilateral pupillary dilatation loss of light reflex stiff ness of the neck bilateral Babinski signs and a cerebrospinal fluid pressure greater than 300 mm Hg (Aring and Hewitt)

Treatment—Consideration of treatment must be limited to massive hemorrhage not because the minor varieties are not inter esting and important but because we know nothing of their diagno sis and in undertaking treatment it should be recognized that a fatal outcome is the rule and recovery an exception

After diagnosis of cerebral hemorrhage is established little of a specific nature can be done for the patient Sudden death is rarely due to hemorrhage unless it occurs into the ventricles or medulla, hence there usually is a period during which the outcome is uncer tain Whether treatment during this period alters the prognosis is not established The old fashioned heroic bleeding of 1 L or more perhaps deserves more thorough study Oxygen may inhibit the spread of cerebral damage

The patient should be placed in a bed equipped with side boards The head should be slightly elevated and turned to one side so the tongue does not fall back into the throat If convulsions occur they should be stopped by venesection or careful administration of magnesium sulfate (p 239) Difficulty in breathing is sometimes met by lowering the head placing an airway and aspirating secre tions Atropine may be used to dry the bronchi

An attempt may be made to reduce the edema of the brain by intravenous injection of 50 per cent sucrose or 25 per cent mannitol (p 239) With 300–500 cc of sucrose Murphy has obtained prompt and prolonged reduction of cerebrospinal fluid pressure as

sociated with profuse diuresis Headache vomiting and vertigo may also be relieved Salt poor hypertonic serum albumin should in theory have a lasting effect Lumbar puncture is performed for diagnostic purposes at first If a large amount of bloody fluid is obtained under increased pressure the puncture may be repeated with benefit particularly when the increased intracranial pressure is in part due to blood which has ruptured into the ventriculosubarachnoid space

Usually no sedatives are required. Rather oxygen by tent and caffeine sodium benzoate 0 5 Gm (7½ gr) every two hours may speed the return to consciousness Hypostatic congestion should be avoided by turning the patient in bed every hour Bed clothes must be kept dry to prevent bed sores During the first few days it is usually necessary to insert an indwelling catheter and tidal drainage is sometimes necessary Hygiene of the mouth is important. Tube feeding is sometimes necessary Penicillin may be given as a prophylactic against pulmonary and genitourinary infections

Some patients have been treated surgically when there was definite evidence of persistently increased *intracerebral* pressure or when the symptoms seemed to be those of tumor A few patients may be benefited simply by aspiration of the old blood through a perforator opening but an osteoplastic flap is usually necessary We have had no experience with this type of treatment The selection of patients for decompression involves keen neurosurgical knowledge Cervical sympathetic block on the side of the lesion is claimed to speed recovery and *in particular* may relieve distressing sensory phenomena such as paresthesias and thalamic pain (Gardner and Nosik)

As convalescence begins gentle massage should be instituted and the skin carefully cared for to avoid bed sores Evidences of phlebothrombosis should be looked for daily in the legs should they become evident venous ligation rather than anticoagulant therapy should be considered Above all the physician and attend

known to need repetition here Of the several apoplexy aphorisms offered by Adams and Cohen one succinctly applies Apoplexy which causes sudden onset of headache confusion then deep coma hemiplegia and bloody cerebrospinal fluid under increased pressure is usually due to spontaneous cerebral hemorrhage Compared to thrombosis cerebral hemorrhage more often causes conjugate deviation unilateral pupillary dilatation loss of light reflex stiffness of the neck, bilateral Babinski signs and a cerebrospinal fluid pressure greater than 300 mm Hg (Aring and Hewitt)

Treatment—Consideration of treatment must be limited to massive hemorrhage not because the minor varieties are not interesting and important but because we know nothing of their diagnosis and in undertaking treatment it should be recognized that a fatal outcome is the rule and recovery an exception

After diagnosis of cerebral hemorrhage is established little of a specific nature can be done for the patient Sudden death is rarely due to hemorrhage unless it occurs into the ventricles or medulla hence there usually is a period during which the outcome is uncertain Whether treatment during this period alters the prognosis is not established The old fashioned heroic bleeding of 1 L or more perhaps deserves more thorough study Oxygen may inhibit the spread of cerebral damage

The patient should be placed in a bed equipped with side boards The head should be slightly elevated and turned to one side so the tongue does not fall back into the throat If convulsions occur they should be stopped by venesection or careful administration of magnesium sulfate (p 239) Difficulty in breathing is sometimes met by lowering the head placing an airway and aspirating secretions Atropine may be used to dry the bronchi

An attempt may be made to reduce the edema of the brain by intravenous injection of 50 per cent sucrose or 25 per cent mannitol (p 239) With 300–500 cc of sucrose Murphy has obtained prompt and prolonged reduction of cerebrospinal fluid pressure as

will have so much foot drop that they will require a short leg brace to help them along As retraining advances ambulation is helped by instruction in the use of crutches usually using the alternate four

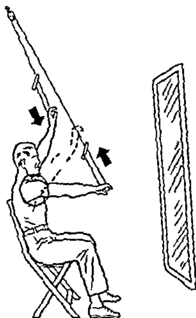


FIG. 4—Pass e pulley exercises in front of mirror will prevent adhesions and ncrease shoul ler movement and control (Courtesy of J G G Deaver and K G Peterson Arch Phys Med 27 17 1946)

point gait as progress is made, instruction is given in climbing steps curbs and ramps

Numerous variations from this basic plan can be thought of Thus Lowman has recommended early active exercises under water in a Hubbard tank for 30 *minutes* three to six times weekly The methods are chosen to suit the needs and capacities of the patient, since the all important aspect of treatment at this time is the main

ants should encourage the patient to take a hopeful view of the outcome

Efforts must now rapidly be directed toward rehabilitation and retraining The outline which follows is taken from the plan proposed by Howard Rusk, whose programs of rehabilitation have been outstandingly successful (Dinken)

First there is the problem of preventing deformities To this end (1) a footboard or a posterior leg splint is used to prevent foot drop, (2) sand bags are placed to retrain outward rotation of the leg on the affected side, (3) adduction of the shoulder is prevented by a small pillow in the axilla and (4) the foot and leg are braced so that strength is maintained in the quadriceps (5) Sitting in bed gives training in balance (6) Aphasia is met by early speech therapy

The next phase is retraining In essence this is passive movement of the affected limbs against a weight suspended on a pulley attached to a gooseneck pipe over the head of the bed The rope is secured to the hand or leg with 1 in webbing While a wide variety of pulley exercises can be devised those described by Deaver and Peterson will be found most useful Their advantage over the customary exercises is that they are passive but still controlled by the patient who knowing the limits of his pain and stretch thresholds will more rapidly achieve a maximum of motion The range of motion is thus continually increased to tolerance Disabling joint adhesions and contractures are prevented while the patient s morale improves as he sees his own progress As soon as possible the patient is encouraged to sit erect to improve his balance Speech reeducation can then begin under the supervision of an experienced teacher

The next stage is ambulation It starts by practicing balance by standing at first with aid and then between parallel bars Normal walking habits and reciprocal leg motion are helped by developing a heel and toe gait thus minimizing clonus About half the patients

Prodromes may occur especially if the clot begins in the small branches of an artery and extends to the main channel but the onset may occur without much warning when the clot forms in a large artery As a result of the obstruction an area of the brain becomes infarcted with edema widespread in the vicinity of the lesion As the edema passes off the area of ischemia is decreased by the restoration of existing vascular beds and the development of collaterals The zone of most severe ischemia finally demarcates and necroses As the necrotic tissue is absorbed it leaves small cystic cavities to mark the lesion

The signs and symptoms of thrombosis obviously depend on the position of the clot These need not detain us here except to point out certain general characteristics Jacksonian convulsions sometimes occur at the onset they indicate thrombosis rather than hemorrhage Sudden severe headache with vomiting immediate unconsciousness abnormalities of the respiration or of the eyes stiffness of the neck and marked leukocytosis all suggest hemorrhage in contrast to thrombosis Bloody *cerebrospinal* fluid under increased pressure is rare in thrombosis and usual *in* hemorrhage

The treatment of thrombosis is much like that of hemorrhage (p 230) Anticoagulants—heparin and dicumarol*—may have value but until more is known of the mechanism and diagnosis of the apoplexies we shun their use Among the vasodilators we have tried papaverine with possibly beneficial effects Nicotinic acid has been recommended Probably the best and certainly most physiologic stimulus to cerebral vasodilation is *inhalation* of CO (2–5 per cent) It should be used experimentally at least when the diagnosis of cerebral thrombosis is well established and may do good after organization of a hemorrhage

Homolateral block of the cervical sympathetic chain after cerebral embolism or thrombosis has been tried in the hope that interruption of sympathetic impulses would diminish vasospasm around the lesion and increase blood flow on the affected side (Volpitto

tenance of an ordered and progressive program which will restore to the patient the ability to enjoy life as more than a hulk While the aid of a competent therapist should be sought whenever possible, in many cases the program must be administered by an attentive nurse or an interested and instructed member of the family

Cerebral Thrombosis

Cerebral thrombosis like cerebral hemorrhage is caused by morbid changes in the vessel walls hence either or both may occur in the same patient Thrombosis often precedes hemorrhage in those who have had several strokes It tends to occur when the blood pressure is reduced and the blood flow less rapid as during sleep after surgery severe exposure or during cachectic states

Some clinicians believe that the usual cause of thrombosis is lowered blood pressure This is sometimes true when the lowering is sufficiently rapid and severe in the presence of vascular damage But this must be infrequent for we have seen the blood pressure profoundly lowered during severe allergic reactions in many malignant hypertensives and have observed thrombosis in only a single case That gradual lowering of blood pressure over days or weeks does not initiate thrombosis is testified to by the results of sympathectomy or kidney extract injection Therefore the dictum that cerebral thrombosis is due to lowering of the arterial pressure has no more than occasional application

What may be a striking example of the effect of lowered pressure with slowed circulation has been reported in a patient who had a hypersensitive carotid sinus Bilateral thrombosis of the anterior cerebral arteries occurred a few minutes after a test stimulation No doubt the vessels had previously been damaged by sclerosis Other cases have followed this one into the literature But the mechanism of thrombosis induced by carotid compression may include reflex effects which do not occur in a simple decrease of arterial pressure

Prodromes may occur especially if the clot begins in the small branches of an artery and extends to the main channel but the onset may occur without much warning when the clot forms in a large artery As a result of the obstruction an area of the brain becomes infarcted with edema widespread in the vicinity of the lesion As the edema passes off the area of ischemia is decreased by the restoration of existing vascular beds and the development of collaterals The zone of most severe ischemia finally demarcates and n croses As the necrotic tissue is absorbed it leaves small cystic cavities to mark the lesion

The signs and symptoms of thrombosis obviously depend on the position of the clot These need not detain us here except to point out certain general characteristics Jacksonian convulsions some times occur at the onset they indicate thrombosis rather than hemorrhage Sudden severe headache with vomiting immediate unconsciousness abnormalities of the respiration or of the eyes stiffness of the neck and marked leukocytosis all suggest hemor rhage in contrast to thrombosis Bloody cerebrospinal fluid under increased pressure is rare in thrombosis and usual in hemorrhage

The treatment of thrombosis is much like that of hemorrhage (p 230) Anticoagulants—heparin and dicumarol[8]—may have value but until more is known of the mechanism and diagnosis of the apoplexies we shun their use Among the vasodilators we have tried papaverine with possibly beneficial effects Nicotinic acid has been recommended Probably the best and certainly most physiologic stimulus to cerebral vasodilation is inhalation of CO (2-5 per cent) It should be used experimentally at least when the diagnosis of cerebral thrombosis is well established and may do good after organization of a hemorrhage

Homolateral block of the cervical sympath tic chain after cere bral embolism or thrombosis has been tried in the hope that inter ruption of sympathetic impulses would dimin sh vasospasm around the lesion and increase blood flow on the affected side (Volpitto

and Risteen Gilbert and de Takats) The onset of Horners syndrome indicates that the injection has been properly placed These blocks should be repeated once or twice daily as long as improvement continues De Takats finds such blocks most effective when given as an emergency treatment in the first hour or two after thrombosis or embolism, but W J Gardner of the Cleveland Clinic earnestly recommends a routine trial of block at any stage in the evolution of the residues of apoplexy Further, he has observed dramatic relief of thalamic pain The blocks may facilitate rehabilitation since they seem to favor the recovery of normal sensation and movement, especially in the legs

Hypertensive Encephalopathy

Hypertensive encephalopathy, as described by Volhard and Oppenheimer and Fishberg somewhat resembles an epileptic seizure with which at times it is carelessly confused Prodromes may or *may not be present, when present they consist of severe and almost* constant headache, nausea vomiting and somnolence Loss of appetite and disturbed sleep may occur a few days before the attack Paresthesias are not uncommon Pallor is often striking The arterial pressure usually rises often to great heights and the urinary volume may fall The pulse is often slow Changes in personality may be evident several days before the attack especially increase in irritability

So heralded or without prodromes the dramatic part of the attack may begin Some patients have violent convulsions with loss of consciousness much like those in eclamptogenic toxemia or epilepsy *Vision may be lost for several hours or days* but the loss is not permanent The profound disturbance of the nervous system is reflected in the development of a Babinski reflex and rigidity of the neck accompanied by a Kernig sign

Other patients rapidly pass into deep coma with slow and stertorous breathing and feeble circulation From this they may

rouse and appear almost normal in 12 or more hours The spinal fluid shows no blood offering evidence that much of the brain is free of gross hemorrhage Spinal fluid pressure is usually greatly increased though this is not an invariable rule. The rapid and often great rise in both systolic and diastolic pressures and the heavy burden thrown on the heart by the convulsion may precipitate acute myocardial insufficiency and death from circulatory failure or pulmonary edema

Volhard found the cerebral symptoms correlated not with impairment of renal function but with rise in blood pressure and vasoconstriction. This important observation differentiates the clinical picture clearly from the coma and convulsions of uremia. The constancy of association of the encephalopathy with increased blood pressure and the frequency of a sharp rise in pressure before the convulsion suggested to Fishberg that the hypertension or the phenomena concerned in its production are causally related to the syndrome This is also suggested by similarity of the syndrome as it may occur in glomerulonephritis and essential hypertension to that in eclampsia

The pathogenesis of the syndrome is uncertain Fishberg who has given the matter the most attention suggests as a *working hypothesis* that when the rise in arterial pressure is sudden or extreme adaptation of the cerebral vessels to the arterial pressure may be defective in either or both of two ways (1) The cerebral arterioles may not constrict as forcefully as necessary to keep pace with the general rise in arterial pressure resulting in increased pressure in the cerebral capillaries and consequent development of edema. (2) Individual vessels may react to rise in pressure by intense spasm with ischemia of the adjacent portion of the brain and focal cerebral symptoms This would occur most often in the presence of marked cerebral arteriosclerosis

There is certainly much indirect evidence suggesting the occurrence of abnormal vasoconstriction during the syndrome but it is

far from being proved The concept of the special irritability of sclerotic foci was ably attacked by Allbutt and by Pickering

Again the occurrence of edema of the brain remains to be proved If focal edema occurs it might easily explain many of the signs and symptoms The fact that hypertonic sugar solutions are so valuable in treatment adds indirect evidence to the validity of this view Scheinker's syndrome of cerebral swelling seems to overlap that of hypertensive encephalopathy and in so doing to offer some substance to the view that the cause is edema of the brain local or diffuse

A valuable study should be made to determine whether hypertensive encephalopathy is not based on constitutional dysrhythmia of the electrical brain waves as in epilepsy It may well be that the rise in arterial pressure acts as the trigger mechanism to initiate the attack The differences in these seizures from those of epilepsy due to cerebral scars might be due simply to the substrate on which the seizure plays

If the patients do not die during an attack—and usually they do not if adequately treated—recovery from the episode is complete This suggests but does not prove that hemorrhages thrombi and focal areas of necrosis probably are not the basis of the syndrome

What many clinicians speak of as hypertensive encephalopathy is a chronic progressive disease quite unlike the episodic crisis just reviewed The state to which we refer is characterized by headache memory loss attenuation of mental acuity personality change and is episodic only in that transient severe motor or sensory disturbances do occur The course is relentlessly downward usually to sudden death from apoplexy Autopsy reveals diffuse areas of cerebral softening foci of extravasation areas of gliosis and cyst formation The process is evidently due to arterio and arteriolosclerosis

Treatment—Fishberg has recommended venesection in almost all patients with severe encephalopathy especially during the prodromal period Usually 500 cc of blood should be removed re

peated in a day or two if necessary It is not clear why venesection is of value especially since the resultant fall in arterial pressure may be slight and transient Transitory reduction in blood volume may benefit by causing fluid from edematous brain to flow from tissue spaces into the blood stream

Lumbar puncture is a measure occasionally valuable and rarely spectacular (Fishberg) although diagnostically important

Hypertonic sucrose or mannitol solutions produce a prolonged fall in intracranial pres ure with little or no secondary rise whereas a secondary rise is common after 50 per cent glucose solution In adults 200–600 cc of 25 per cent mannitol may be given by slow intravenous infusion This may be followed up by several further injections of 100 cc during the next 24 hours Such treatment often stops the convulsions immediately Treatment with sucrose should not be prolonged over a period of days because of the danger of tubular cell injury Mannitol does not appear to share this injurious action As noted previously large doses of salt poor albumin may prove still more effective in the treatment of cerebral edema However in this syndrome its effect and that of other modes of treatment is difficult to evaluate partly because of the episodic nature of the ailment

Administration of a solution of magnesium sulfate during the stage of headache and vomiting may prevent convulsions as in eclampsia In adults 20 cc of a 10 per cent solution may be given intravenously very slowly and in children 10 cc per kg of body weight of a 2 per cent solution This may be repeated at two hour intervals or if the attack is severe even once an hour with due attention to the tendon reflexes respiratory rate and the rate of urine formation

In mild cases the dosage is 30–60 cc for children and 60–100 cc of 50 per cent solution for adults given by rectum every four or five hours as indicated by the state of the patient More severe cases may require intramuscular injections of 0 2–0 4 cc per kg of

far from being proved The concept of the special irritability of sclerotic foci was ably attacked by Allbutt and by Pickering

Again, the occurrence of edema of the brain remains to be proved If focal edema occurs, it might easily explain many of the signs and symptoms The fact that hypertonic sugar solutions are so valuable in treatment adds indirect evidence to the validity of this view Scheinker's syndrome of cerebral swelling seems to overlap that of hypertensive encephalopathy and in so doing to offer some substance to the view that the cause is edema of the brain local or diffuse

*A valuable study should be made to determine whether hyper*tensive encephalopathy is not based on constitutional dysrhythmia of the electrical brain waves as in epilepsy It may well be that the rise in arterial pressure acts as the trigger mechanism to initiate the attack The differences in these seizures from those of epilepsy due to cerebral scars might be due simply to the substrate on which the seizure plays

If the patients do not die during an attack—and usually they do not if adequately treated—recovery from the episode is complete This suggests but does not prove that hemorrhages thrombi and focal areas of necrosis probably are not the basis of the syndrome

What many clinicians speak of as hypertensive encephalopathy is a chronic progressive disease quite unlike the episodic crisis just reviewed The state to which we refer is characterized by headache memory loss attenuation of mental acuity personality change and is episodic only in that transient severe motor or sensory disturbances do occur The course is relentlessly downward usually to sudden death from apoplexy Autopsy reveals diffuse areas of cerebral softening foci of extravasation areas of gliosis and cyst formation The process is evidently due to arterio and arteriolosclerosis

Treatment—Fishberg has recommended venesection in almost all patients with severe encephalopathy especially during the prodromal period Usually 500 cc of blood should be removed re

pea ed in a day or two if necessary It is not clear why venesection is of value especially since the resultant fall in arterial pressure may be slight and transient. Transitory reduction in blood volume may benefit by causing fluid from edematous brain to flow from tissue spaces into the blood stream

Lumbar puncture is a measure occasionally valuable and rarely spectacular (Fishberg) although diagnostically important.

Hypertonic sucrose or mannitol solutions produce a prolonged fall in intracranial pressure with little or no secondary rise whereas a secondary rise is common after 50 per cent glucose solution In adults 200–600 cc of 25 per cent mannitol may be given by slow intravenous infusion This may be followed up by several further injections of 100 cc during the next 24 hours Such treatment often stops the convulsions immediately Treatment with sucrose should not be prolonged over a period of days because of the danger of tubular cell injury Mannitol does not appear to share this injurious action. As noted previously large doses of salt poor albumin may prove still more effective in the treatment of cerebral edema However in this syndrome its effect and that of other modes of trea ment is difficult to evaluate partly because of the episodic nature of the ailment

Administration of a solution of magnesium sulfate during the stage of headache and vomiting may prevent convulsions as in eclampsia In adults 20 cc of a 10 per cent solution may be given intravenously very slowly and in children 10 cc per kg of body weight of a 2 per cent solution This may be repeated at two hour intervals or if the attack is severe even once an hour with due attention to the tendon reflexes respiratory rate and the rate of urine formation

In mild cases the dosage is 30–60 cc for children and 60–100 cc of 50 per cent solution for adults given by rectum every four or five hours as indicated by the state of the patient. More severe cases may require intramuscular injections of 0.2–0 4 cc per kg of

body weight of 25 per cent solution for children and a total dose of 10–15 cc for adults

If respiratory depression occurs after magnesium sulfate administration and this is rare, it can be relieved by the intravenous injection of 5 per cent solution of calcium chloride or calcium gluconate in 20–30 cc doses

If convulsions are severe and difficult to control, a small intravenous injection of pentothal sodium® has merit It should be given slowly and only enough to control the current seizure Neither morphine nor chloroform seems to have any particular place in the treatment of this syndrome If a sedative is needed one of the longer acting barbiturates may be given—by rectum if necessary contained in a pin perforated gelatin capsule

In the face of impending cardiac failure treatment follows that described (*pp 210 ff*)

Papaverine recommended as possibly of value in cerebral thrombosis has been advocated to prevent the less severe transient cerebral seizures which Russek and Zohman attributed to angiospasm It is given orally in doses ranging from *0 3* to *1 2 Gm* (4½–18 gr) alone or with phenobarbital The advantage of mild sedation is suggested by the fact that tea and coffee impair the value of papaverine in cerebrovascular disease

Aminophylline 0 1–0 2 Gm four times daily has been recommended by Reese and Kant as a cerebral vasodilator for use in cerebral arteriosclerosis and so called hypertensive encephalopathy Although it may be helpful it is not likely that the drug thus used does cause a significant cerebral vasodilation

Vertigo

Vertigo is the sensation that the outer world is moving about the patient or that the patient is moving in space It is not dizziness or giddiness As a rule it has no relation to syncope Fortunately it is not common in hypertensives but it causes real suffering and

its presence usually indicates that hemorrhages albeit small ones have occurred in the brain

Since vertigo may arise from a wide variety of foci i.e the labyrinth itself the vestibular nerve the vestibular centers or central nervous connections it is exceedingly difficult to ascertain its mechanism in the hypertensive patient. Presence of nystagmus may be an aid Spontaneous vertical nystagmus suggests lesions in the brain stem. The phenomenon of past pointing speaks for cerebellar disease There are other tests for abnormal labyrinthine functions but they require the services of a specialist both for their performance and for their interpretation

Sedatives such as phenobarbital and bromide in small doses may have some value in alleviating the distress Since there is thought to be some similarity of the vertigo of hypertension and that of Meniere s disease the treatment of the latter has been tried in the former Furstenberg had good results from a low sodium diet and administration of six capsules of 0 48 Gm. (7½ gr) ammonium chloride with meals for three days and then a rest period for two days He believes that a lesion is present in the labyrinth which allows retention of sodium ions thus producing pressure alterations which cause the vertigo Talbott and Brown obtained equally good results in Meniere s disease with diets of normal sodium content and hence concluded that the sodium ion was not the precipitating cause of acute attacks They administer 6–10 Gm. of potassium chloride daily Potassium nitrate may be substituted for potassium chloride These various procedures deserve a trial but there is no assurance of success We find nicotinic acid in 50 or 100 mg doses as tolerated, four times daily more valuable than any of the foregoing

Syncope which is primarily dependent on disturbances of cerebral circulation, usually occurs while the patient is upright When it develops while the patient is in the horizontal position it is usually serious Fortunately it is rare in hypertensives except in those de

body weight of 25 per cent solution for children and a total dose of 10–15 cc for adults

If respiratory depression occurs after magnesium sulfate administration, and this is rare it can be relieved by the intravenous injection of 5 per cent solution of calcium chloride or calcium gluconate in 20–30 cc doses

If convulsions are severe and difficult to control, a small *intravenous injection of pentothal sodium®* has merit *It should be* given slowly and only enough to control the current seizure Neither morphine nor chloroform seems to have any particular place in the treatment of this syndrome If a sedative is needed one of the longer acting barbiturates may be given—by rectum if necessary, contained in a pin perforated gelatin capsule

In the face of impending cardiac failure treatment follows that described (pp 210 ff)

Papaverine recommended as possibly of value in cerebral thrombosis has been advocated to prevent the less severe transient cerebral seizures which Russek and Zohman attributed to angiospasm It is given orally in doses ranging from 0 3 to 1 2 Gm (4½–18 gr), alone or with phenobarbital The advantage of mild sedation is suggested by the fact that tea and coffee impair the value of papaverine in cerebrovascular disease

Aminophylline 0 1–0 2 Gm four times daily has been recommended by Reese and Kant as a cerebral vasodilator for use in cerebral arteriosclerosis and so called hypertensive encephalopathy Although it may be helpful it is not likely that the drug thus used does cause a significant cerebral vasodilation

VERTIGO

Vertigo is the sensation that the outer world is moving about the patient or that the patient is moving in space It is not dizziness or *giddiness As a rule it has no relation to syncope Fortunately* it is not common in hypertensives but it causes real suffering and

The first and typical headache in hypertension is a dull diffuse deep ache Especially at the outset the pain is throbbing It usually develops in the small hours of the morning and may be intense enough to awaken the patient The site varies pain may be generalized lateral or occipital Getting up out of bed sitting up in a chair dressing taking coffee and beginning the duties of the day often give relief at least in part. Some patients have some relief from sleeping in the head up position with the head of the bed raised on chairs or blocks Most forms of bodily effort particularly stooping and coughing increase the pain momentarily Digital compression of the common carotid occipital frontal postauricular or temporal arteries relieves the pain when the site of headache can be localized Ergotamine tartrate (0 25–0 5 mg intramuscularly) relieves the pain although it may increase arterial pressure The fact that this drug acts primarily on the branches of the external carotid artery and the effect of digital compression indicate that this type of headache like that of migraine is caused by distention of external carotid branches Indeed ligation of the temporal artery may decrease the intensity of headache for some months

The fact that this type of headache is akin to migraine was first indicated by Janeway in 1913 He found that a large number of patients who complained of hypertensive headaches had had migraine throughout life Since the headache appears in many patients after the onset of hypertension but without definite relation to the level of arterial pressure it is probable that in some a decreased contractive power of the arteries comfortable enough when the blood pressure is normal results in painful distention of the vessel wall when the pressure is elevated The association with migraine has a further corollary that in migrainous people as in patients with hypertension the frequency and severity of headache is closely related to states of emotional tension

The second type of headache in hypertension often coexistent with the first, is characterized by pain and stiffness localized to the

veloping orthostatic hypotension following sympathectomy The possibility that syncope is the result of a hyperactive carotid sinus should not be overlooked

Dizziness and giddiness are terms restricted to an abnormal sensation of unsteadiness characterized by a feeling of movement within the head According to Soma Weiss dizziness is often a forme fruste of syncope Nicotinic acid may be given as for vertigo Injections of histamine (0 05 cc of 1 1 000 solution) once or twice a week have been recommended by Marshall The dose may be increased by increments of 0 1 cc to a maximum of 0 5 cc if tolerance develops Both androgen and estrogen therapy have been recommended to increase cerebral circulation but too little experience is available to provide a basis for the determination of their value In brief treatment is unsatisfactory Possibly greater attention should be paid to the probable psychogenic origin of these symptoms

Headache

Owing largely to the studies of Wolff the mechanism of the headache in hypertension is well on the way to being understood First let us make it clear that although there is a relationship between the height of the blood pressure and the occurrence of headache it is not a direct one Thus about half of hypertensive patients do not have headaches In others headaches began before hypertension was present Headaches disappear in some patients without changes in blood pressure this is often striking after lumbodorsal sympathectomy Despite these facts there can be little doubt that headache is more common among hypertensive patients than among normotensives

A misconception exists that headache in hypertension is necessarily associated with high intracranial tension This is almost certainly not true It is important to realize this because the misconception has led to spinal taps as a means of giving relief

these muscle tension headaches should be recognized and treated appropriately

Nitrites should not be given They usually make the headache worse not better Spinal puncture rarely has a beneficial effect and may make the headache worse Venesection is said to relieve severe obdurate headache but we have never needed to use it

Dorsolumbar sympathectomy often gives surprising relief even when arterial pressure is not significantly reduced This is a benefit of sympathectomy not to be dismissed lightly but is not in itself an indication for operation

BIBLIOGRAPHY

ADAMS R D AND COHEN M F Vascular diseases of the brain Bull New England M. Center 9 180 222 261 1947

COBB S AND BLAIR D in Cowdry E V Arteriosclerosis (New York The Macmillan Company 1933)

DAVISON C AND BRILL N Q Essential hypertension and chronic hypertensive encephalopathy A clinico-pathologic study *Ann. Int. Med.* 12 1766 1939

DEAVER J G G AND PETERSON K G Pulley exercises to increase joint movement, Arch. Phys Med 27 17 1946

DINKEN H Evaluation of disability and treatment in hemiplegia *Arch Phys. Med* 28 763 1947

JANEWAY A clinical study of hypertensive cardiovascular disease Arch. Int. Med. 12 755 1913

KETY S S *et al* The blood flow vascular resistance and oxygen consumption of the brain in essential hypertension J Clin. Investigation 27 511 1948

LOWMAN E W Rehabilitation of the hemiplegic patient J A. M A. 137 431 1948

MONTEIRO A. A new sign of arterial hypertension Hospital, Rio de Janeiro 16 119 1939

MURPHY F D HIRSHBERG R. A AND KATZ, A M The effect of intravenous injections of sucrose solution (50%) on the cerebrospinal fluid pressure the blood pressure and clinical course in cases of chronic hypertension Am J M Sc 192 510 1936

OPPENHEIMER B S AND FISHBERG A. M Hypertensive encephalopathy Arch Int Med 41 264 1928

PICKERING G W Transient cerebral paralysis in hypertension and in cerebral embolism J A. M A. 13 423 1948

REESE H H AND KANT F The use of aminophylline in neuropsychiatric disorders associated with cerebral arteriosclerosis and hypertensive encephalopathy Am J Psychiat 103 731 1947

ROSENBERG E F Brain in malignant hypertension Clinicopathologic study Arch Int Med 65 545 1940

RUSK H Rehabilitation in general practice J A M A 139 14 1949

nape of the neck the occiput or on up to the vertex Typically, the complaint is of a feeling as if the neck or back of the head were in a vise or clamp or as if a band of iron had been pressed down on the head Inspection may reveal some torticollis or elevation of one shoulder The muscles of the neck are found tight and tender on one or both sides Extremely sensitive small nodules can sometimes be felt in the affected muscles The mechanism of this type of headache is sustained contraction of the muscles This contraction even more obviously than the first type of headache arises on a basis of emotional stress and strain

Finally, in patients with renal failure and malignant hypertension headache may appear which is diffuse has no relation to posture and is only infrequently decreased by the removal of cerebrospinal fluid Intravenous injections of glucose sucrose or mannitol usually give temporary relief

Treatment of headache in hypertension is on the whole rather satisfactory, and all the more so when the mechanism of the headache is understood For slight headaches aspirin (0 3–0 6 Gm) is usually adequate Aminopyrine seems to be more effective in some patients Codeine (60 mg) can be given at times when pain is more intense Two remedies remain which are extraordinarily effective One is rest in bed and as suggested sometimes in a head up bed prolonged over several days The other is potassium thiocyanate given properly (p 320) In using any of these it is important to remember that remedies for headache act best when taken in adequate dosage early in the course of the pain

Headache due to muscular contraction responds to these and other measures including *a prolonged hot bath the use of a heat* lamp or heating pad and massage When tender nodules are palpable procaine can be injected near them often with dramatic and sometimes with lasting effect Wolff has pointed out that such injections deep into the muscles of the neck can be very dangerous

For the rest the strong psychic and emotional components of

these muscle tension headaches should be recognized and treated appropriately

Nitrites should not be given They usually make the headache worse not better Spinal puncture rarely has a beneficial effect and may make the headache worse Venesection is said to relieve severe obdurate headache but we have *never needed to use it*

Dorsolumbar sympathectomy often gives surprising relief even when arterial pressure is not significantly reduced This is a benefit of sympathectomy not to be dismissed lightly but is not in itself an indication for operation

BIBLIOGRAPHY

ADAMS R. D AND COHEN M. F Vascular d seases of the brain Bull New England M. Center 9 180 222 261 1947

COBB S AND BLAIR, D in Cowdry E. V Arteriosclerosis (New York The Macmillan Company 1933)

DAVISON C AND BRILL N Q Essential hypertens on and chronic hypertensive encephalopathy A clinico-pathologic study Ann. Int. Med. 12 1766 1939

DEAVER, J G G AND PETERSON K G Pulley exercises to increase joint movement, Arch. Phys Med. 27 17 1946.

DINKEN H Evaluation of disability and treatment in hemiplegia, Arch. Phys Med 28 263 1947

JANEWAY A clinical study of hypertensive cardiovascular disease Arch. Int. Med. 12 755 1913

KETY S S *et al* The blood flow vascular res stance and oxygen consumption of the brain in essential hypertension J Clin. Investigation 27 511 1948

LOWMAN E. W Rehabilitation of the hemiplegic patient J A M A. 137 431 1948

MONTEIRO A. A new sign of arterial hypertension Hospital Rio de Janeiro 16 119 1939

MURPHY F D HIRSCHBERG R. A. AND KATZ, A M The effect of intravenous injections of sucrose solution (50%) on the cerebrospinal fluid pressure the blood pressure and clinical course in cases of chronic hypertension Am. J M. Sc. 192 510 1936

OPPENHEIMER B S AND FISHBERG A. M. Hypertensive encephalopathy Arch Int. Med 41 264 1928

PICKERING, G W Trans ent cerebral paralysis in hypertension and in cerebral embolism J A. M A 137 423 1948

REESE, H H AND KANT F The use of aminophylline in neuropsychiatric d sorders associated with cerebral arteriosclerosis and hypertensive encephalopathy Am J Psychiat. 103 731 1947

ROSENBERG E. F Brain in malignant hypertens on Clinicopathologic study Arch. Int. Med. 65 545 1940

RUSK, H Rehabilitation in general practice J A. M A. 139 14 1949

RUSSEK H I AND ZOHMAN B L Papaverine in cerebral angiospasm (vascular encephalopathy) J A M A 136 930 1938
SCHEINKER I M Alterations of cerebral capillaries in the early stages of arterial hypertension Am J Path 24 211 1948
——— Hypertensive cerebral swelling A characteristic clinico pathologic syndrome Ann Int Med 28 630 1948
SCHMIDT C F The present status of knowledge concerning the intrinsic control of the cerebral circulation and the effects of functional derangements on it Federation Proc 3 131 1944
VOLHARD F in von Bergmann G and Stahelin R. (eds) *Handbuch der inneren Medizin* Vol 6 (2d ed Berlin Julius Springer 1931)
WEISS S AND BAKER J P The carotid sinus reflex in health and disease Its role in the causation of fainting and convulsions *Medicine 12 297 1933*
WOLFF H G Headache and Other Head Pain (New York Oxford University Press 1948)

12 The Kidneys in Hypertension

I FUNCTION PATHOGENIC PARTICIPATION

THE IMPORTANCE OF the renal vasculature is obvious from the fact that it accounts for about one fifth of the total peripheral resistance while the kidneys account for less than 1 per cent of the body weight The intense vascularity of the kidneys is not obvious after death as it is in spleen and liver This is partly due to rigor of the muscular walls of the renal arterial and arteriolar vessels This myriad of channels is almost specifically susceptible to the destructive influences of severe or prolonged hypertension Injury results in parenchymal loss and establishes a relation between renal injury and hypertension which has been recognized since the time of Bright

But, since the sequence of events has remained obscure concepts of the genesis of hypertension have developed in cycles which differ as they ascribe more or less importance to the kidneys as the primary agent (Table 10) Thus the cycle has in a century gone the full course and returned to the kidney As long as renal function was considered only in terms of excretion and this function was normal or nearly so in many cases of hypertension the possibility that renal injury caused onset of the disease seemed implausible The fact that the kidney has endocrine as well as exocrine functions has partly closed this gap Recent advances in the study of renal excretory function have also been brought to bear on the problem

FORMATION OF URINE

The ultimate components of the kidney are blood vessels, epithelial cells and fibrous stroma. These join together in the unit of kidney structure, the nephron. Each nephron is, in microcosm, a kidney, and the whole kidney consists of an orderly, space saving arrangement of more than a million nephrons. The concepts of

TABLE 10.—CONCEPTS AND COGNOMENS IN HYPERTENSION

PHASE	AUTHOR	COGNOMEN	ATTRIBUTED CAUSE
A *Renal*			
	Bright (1827)	Albuminous urine, etc	Renal (hypertension assumed)
	Johnson (1868)	Bright's disease	Renal
B *Arteriosclerosis, small vessels*			
	Gull and Sutton (1872)	Arteriocapillary fibrosis	Generalized
	Mahommed (1872)	Pre albuminuric Bright's disease	Generalized
	von Basch (1893)	Latent arteriosclerosis	Generalized
	Huchard (1899)	Presclerosis	Generalized
C *Vascular hypertension*			
	Allbutt (1896, 1915)	Hyperpiesia	Vasomotor (?)
	Janeway (1907)	Essential hypertension	Vasomotor
D *Arteriosclerosis affecting vasomotor mechanisms*			
	Starling (1925)	Presumed arteriosclerosis of vasomotor center	
	Bordley Baker (1926)	Similar concept with demonstration	
E *Renal arteriolosclerosis*			
	Volhard (1918)	Nephrosclerosis	Generalized and renal
	Goldblatt (1933)	(Experimentally shown)	Renal ischemia

renal function are therefore most simply considered in terms which visualize, for illustration, the whole kidney as a single nephron and the renal artery and all its branches as a single vessel (Figs. 10 and 11). The first component is an arterial vessel which branches to form the afferent arteriole. Around it are dispersed myoepithelial cells which aggregate in cushions close to the glomerulus where they lie in relation to the macula densa of the distal tubule.

blood flow to the cortex while an increased proportion and even an increased volume of blood is forced into the medulla through the juxtamedullary glomeruli, whence it passes to the renal vein In their monograph the authors develop this fact into a hypothesis which would explain post traumatic anurias and even the genesis of hypertension These concepts seem to us overdeveloped Shunting of blood from the cortex is hardly a valid concept since there is no evidence of true shunting of the total renal blood flow but only of cortical ischemia with resultant redistribution of fractional blood flow and a relative or slight absolute increase in volume of blood in the medulla The Trueta phenomenon seems to us an end stage of any severe renal vasoconstriction As such it may occur in patients under severe stimulations of many kinds But shunting has been shown not to be present in hypertensive patients under basal conditions and even under the influence of vasoactive drugs This does not mean that renal vasomotor reactions in hypertensives may not result in cortical ischemia with a relative increase in medullary flow under conditions which would not have this effect in normal people If as the authors suggest renal vasoconstriction of nervous origin were the basic factor in hypertension then renal denervation should be a curative procedure But it is not

Bowman recognized the function of the glomerulus stating a century ago It would indeed be difficult to conceive a disposition of parts more calculated to favour the escape of water from the blood than that of the Malpighian body A large artery breaks up in a very direct manner into a number of minute branches each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself and from which there is but one narrow exit The first step in excretion is filtration from plasma of water and the substances it holds in solution Filtration is a common function of all capillaries glomerular filtration is distinctive because of (1) the anatomic arrangement Bowman described (2) the double capillary walls endothelium + epithelium so that pas

The afferent arteriole abruptly divides into a series of capillary loops all of which are enveloped in a thin epithelial membrane—Bowman s capsule Loops and capsule together form the glomerulus. The capillary loops rejoin and leave the capsule as a thin short, stiff muscular vessel—the efferent arteriole—which typically subdivides into a group of anastomosing capillaries These streams of blood ramify around the epithelial tubules and flow together into venules and veins to leave the kidney Preglomerular arterial channels may lead to peritubular capillaries to a very small extent normally and to greater degree in the presence of renal particularly primarily glomerular disease These preglomerular shunts are branches of afferent arterioles interlobular or capsular arteries Their physiologic significance even in disease is not easy to visualize except as they account for persistence and even hypertrophy of aglomerular tubules in disease

Trueta, Barclay and co-workers have applied new and very graphic technics to the study of renal circulation which emphasize differences between cortical and medullary blood flow The glomeruli in and near the boundary zone between cortex and medulla are the juxtamedullary glomeruli. It has long been known that their structure was different in detail from that of the glomeruli in the cortex proper The basic anatomic difference lies in the fact that the efferent arterioles of the juxtamedullary glomeruli do not arborize into capillaries as do those of the many times more numerous cortical glomeruli Rather they branch into long looping vessels which pass down into the medulla (arteriae verae rectae) and return therefrom as venules with little formation of a capillary meshwork Constriction of the afferent arterioles and interlobular arteries reduces blood flow through the cortex Such constriction can occur in many situations but is apparently best elicited by strong stimulation of renal vasomotor nerves Increased cortical vascular resistance with persistence of blood flow in the interlobar and arcuate arteries decreases total renal blood flow and especially the

blood flow to the cortex, while an increased proportion and even an increased volume of blood is forced into the medulla through the juxtamedullary glomeruli, whence it passes to the renal vein In their monograph the authors develop this fact into a hypothesis which would explain post traumatic anurias and even the genesis of hypertension These concepts seem to us overdeveloped Shunting of blood from the cortex is hardly a valid concept since there is no evidence of true shunting of the total renal blood flow but only of cortical ischemia with resultant redistribution of fractional blood flow and a relative or slight absolute increase in volume of blood in the medulla The Trueta phenomenon seems to us an end stage of any severe renal vasoconstriction As such it may occur in patients under severe stimulations of many kinds But shunting has been shown not to be present in hypertensive patients under basal conditions and even under the influence of vasoactive drugs This does not mean that renal vasomotor reactions in hypertensives may not result in cortical ischemia with a relative increase in medullary flow under conditions which would not have this effect in normal people If as the authors suggest renal vasoconstriction of nervous origin were the basic factor in hypertension then renal denervation should be a curative procedure But it is not

Bowman recognized the function of the glomerulus stating a century ago It would indeed be difficult to conceive a disposition of parts more calculated to favour the escape of water from the blood than that of the Malpighian body A large artery breaks up in a very direct manner into a number of minute branches each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself and from which there is but one narrow exit The first step in excretion is filtration from plasma of water and the substances it holds in solution Filtration is a common function of all capillaries glomerular filtration is distinctive because of (1) the anatomic arrangement Bowman described (2) the double capillary walls endothelium + epithelium so that pas

sage of protein is restricted (3) the high hydrostatic pressure of the capillaries in the order of 60 instead of the 25 mm Hg of the systemic capillary and (4) the outward unidirectional flow of filtrate

Theoretically the volume of glomerular filtrate depends on the balance between the volume of glomerular plasma flow and the filtration pressure the latter usually being the more significant. Filtration pressure is a net value derived from the algebraic summation of (1) a positive value—hydrostatic pressure and (2) opposing values—plasma osmotic pressure renal tissue pressure and the pressure required to force fluid out through the tubules The most important and easily variable factor is hydrostatic pressure Its control rests in the arterioles With a normal constant, systemic arterial pressure constriction of afferent arterioles reduces filtration subsequent constriction of efferent arterioles rebuilds the head and restores filtration

When some stimulus causes systemic arterial pressure to rise to a high level the afferent arterioles constrict presumably to protect the fragile capillaries from the full blast. Filtration rate may then remain unchanged if the afferent constriction is adjusted so as to maintain normal filtration pressure and renal blood flow If to this state of balanced arterial hypertension and renal arteriolar constriction there is added constriction of the efferent arterioles intraglomerular pressure rises while the added vascular resistance tends to decrease renal blood flow Although the plasma minute volume from which the filtrate is expressed is thereby reduced increased filtration pressure may still force a normal volume of water out of the plasma

We conceive of the first of these situations—that of arterial hypertension afferent arteriolar constriction and normal levels of renal blood flow filtration pressure and filtration rate—as that which obtains in the stage of early hypertension in which it seems likely that neural and neurohumoral factors predominate The later stage

—with superimposed efferent arteriolar constriction, reduced renal blood flow, increased filtration pressure but still perhaps a normal filtration rate—is thought of as more consistent with humoral renal pressor activity

Glomerular filtrate is a nearly protein free fluid which contains all the soluble constituents of plasma Normally, about 130 cc is formed per minute Its unchecked discharge to the exterior would cause daily loss of about 200 L water, 1 100 Gm sodium chloride and 270 Gm dextrose, in addition to the numerically less impressive but physiologically highly significant content of other solutes The modification of filtrate into urine prevents this loss This process occurs in the epithelial portion of the nephron, the renal tubule It consists in the reabsorption of water and differentially, of solutes It is completed by the secretion into tubular fluid of certain substances

Several mechanisms participate in reabsorption One is simple osmotic adjustment by which the pull of the concentrated plasma in the peritubular capillaries withdraws water from the tubule fluid But osmosis alone would result in the formation of isotonic (sp gr 1 010) urine of constant volume and content and would lead rapidly to dehydration and demineralization The greater part of reabsorption therefore depends on the activity of the renal tubular cells This restores to the body by cellular chemical work the fluid and needed solutes the mechanical work of the heart had forced through the glomerular capillaries The details of this process may be reviewed in Smith s monographs Briefly water and electrolyte reabsorption are conceived of as developing in two phases which correspond to the major divisions of the tubule In the proximal portion salt and glucose are actively transferred carrying water into the plasma the dilute fluid which enters the thin segment is then brought up to the osmotic concentration of plasma with further loss of water At this stage the fluid volume has been reduced from that of filtrate by about 80 per cent In the distal tubule the

final formation of urine includes further adjustment of its volume according to water needs in part as a result of tubular cell control by posterior pituitary hormone and of its pH by reabsorption of bicarbonate and secretion of ammonia. Formation of urine ends the excretory aspect of *renal function*.

Renal Pressor System and Experimental Renal Hypertension

The *demonstration* by Goldblatt that the kidney can play an other role—that of a causal agent in experimental hypertension—indicates the existence of a function other than excretion one of internal secretion. True the view that the kidney *might actively* cause hypertension through some disturbance of its circulation had been advanced before The problem of credit—if a problem here exists—is easily resolved in the terms cited from Osler applied *previously* to Herrick and here to Goldblatt. He demonstrated that persistent arterial hypertension having many characteristics of essential and malignant hypertension in human beings, can be regularly produced experimentally by *partial compression* of the renal artery within a metal clamp Subsequent studies and the demonstration by others that this renal hypertension does not depend on the action of renal nerves indicates that the mechanism is humoral. A similar state may be more easily induced by *perirenal* application of silk or Cellophane (Figs 5 and 6) The dissociation of renal excretory and pressor-endocrine functions is perhaps best demonstrated in the endocrine *kidney of Selye Here compression* of the aorta between the renal arteries so decreases arterial pressure in the lower (left) renal artery that glomerular filtration ceases But blood *flow persists* and, although the glomeruli ducts and most components of the tubules atrophy part of the proximal tubule hypertrophies This process is associated with hypertension and *severe arterial* disease which runs its course in a few days

The possibility of a renal internal secretion which *might result*



FIG 5 (*above*) —Hypertension results when clamps are applied to the renal arteries This dog developed hypertension with unimpaired renal excretory function (Courtesy of Dr Harry Goldblatt)

FIG 6 (*below*) —Perinephric hull resulting from application of silk or Cellophane to kidney After six weeks arterial pressure was 244 mm Hg

in persistent hypertension has since been resolved into the following propositions (1) Renin a protein present in renal cortex and formed in tubule cells is a proteolytic enzyme (2) The substrate on which renin normally acts is another protein formed in the liver demonstrated in plasma as a constituent of the α globulin (3) The action of renin on renin substrate results in the liberation of a product called angiotonin whose characteristics are those of a polypeptide and the pattern of whose structure has been outlined. Angiotonin causes constriction of smooth muscle it has relatively little action on veins or gut but acts powerfully on arterioles arteries and the myocardium Its formation from renin within the body or its injection as such causes arteriolar constriction, cardiac augmentation and increased arterial pressure When injected into normal persons it produces hypertension with many of the clinical characteristics of essential hypertension. The differences are small but real they perhaps depend on the rate at which the stimulus is provided—suddenly in the normotensive and by slow adjusted increment with chance for adaptation in the hypertensive (Fig 7)

The problem of the pressor system is complicated by the fact (4) that angiotonin is readily altered or destroyed by proteolytic enzymes widely distributed throughout the body Some which act in vitro under conditions compatible with activity in vivo are concentrated in the kidney From this aspect these enzymes are generally referred to as angiotonases Thus apart from the possibility of excess liberation of renin abnormal accumulation of angiotonin in blood may depend on failure of the mechanism which destroys it

Following the initial observation of Kohlstaedt and Page that renin requires a substance contained in plasma for its pressor action Braun Menendez and others of Dr Houssay s institute in Buenos Aires independently developed a similar concept Their nomenclature differs in that renin substrate is spoken of as hypertensinogen angiotonin as hypertensin and angiotonase as hypertensinase

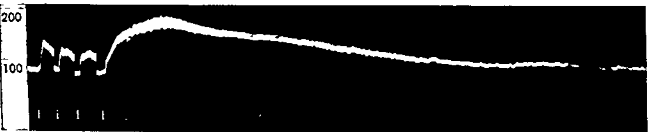


FIG 7.—Effect on arterial pressure of a dog of injections of angiotonin and renin The first three injections were of angiotonin and the last two of renin The sharper rise of pressure and its more transient character are seen after angiotonin administration The more prolonged action of renin is presumably due to slow liberation of angiotonin as the result of the reaction between renin and renin substr te

Relation of Experimental Renal to Clinical Essential Hypertension

The presumption is that experimental renal hypertension is the result of excessive renal pressor activity However the exact mechanisms are not fully established It is not too much to suppose that primary renal (glomerulonephritic, pyelonephritic) hypertension depends on the same mechanism The clinical and pathologic similarities of renal hypertension and of essential hypertension with renal arteriolosclerosis *suggest*, but do not prove the operation of the pressor system in late essential hypertension.

The transition from the special conditions of pyelonephritis and glomerulonephritis which constitute the bulk of undisputed renal hypertension in man to essential hypertension is not easily achieved Typically in early hypertension the solute content and volume of urine are normal Renal excretory function is to outward appearances undisturbed Indeed the concept of essential hypertension and its separation from nephritis depend on this fact. Further the original concept of experimental renal hypertension included the view that it developed and persisted because of renal ischemia it involved the belief that hypertension is a compensation for a reduced volume of renal blood flow But ischemia, a deficiency of blood flow sufficiently abnormal to excite an endocrine mechanism should also result in some decrease of excretory function in an organ which has to do double duty Neither histologic nor functional examinations in cases of early hypertension indicate that ischemia is present rather the methods of measurement of renal blood flow developed by Smith indicate in his hands as in ours that ischemia is frequently absent or demonstrably secondary Renal blood flow of hypertensive subjects is often increased during the fall of arterial pressure to normal levels caused by spinal anesthesia This fact weighs still *further* against the primary role of arteriolosclerosis and the view that hypertension is a compensation for renal

ischemia due to arteriolosclerosis (Fig 8) The analogy between renal hypertension and essential hypertension is thus jeopardized at the outset It seemed that there might be two types of hypertension, one due to renal ischemia and numerically less common, another

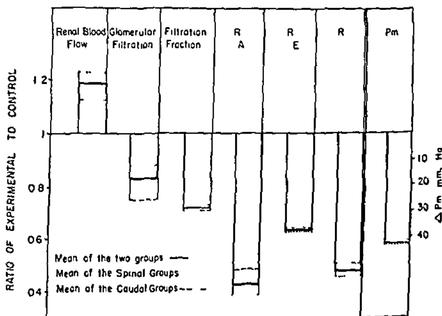


FIG 8—Renal hemodynamics in hypertensive patients during high caudal or spinal anesthesia ratio of experimental to control levels Despite a drop of arterial pressure *Pm* into the normal range renal blood flow is increased because of decreased vascular resistance *R* both afferent R_A and efferent R_E. A residue of abnormal afferent resistance attributable to arteriolosclerosis accounts for most of the fall in filtration rate and fraction The data demonstrate (1) the flexibility and autonomy of the hypertensive s renal vascular bed (2) that hypertension is not a compensation for renal arteriolosclerotic ischemia and (3) that a decrease in blood pressure does not place renal function in jeopardy (Courtesy of Am Heart J 36 226 1948)

not due to primary renal factors or to renal ischemia sufficiently widespread to constitute the great clinical problem of the age

However it has been shown that renal hypertension may be experimentally produced in the absence of persistent renal ischemia

or excretory defect either by renal arterial constriction or by the compression of the kidney in the scar of perinephritis Since this hypertension is undoubtedly renal and presumably the effect of renal pressor activity the independence of renal pressor-endocrine and excretory functions is established. Thus it is possible for the renal mechanism to operate in the clinically significant hypertensive states and in the absence of ischemia. However all experimental methods producing renal hypertension depend on procedures which may in some way modify the flow of blood through the kidney The nature of this change was hinted at by the observation that conversion of renal blood flow from a pulsatile to a continuous type with maintenance of constant renal blood flow results in liberation of renin in the isolated kidney which secondarily becomes ischemic

Thus while renal hypertension sometimes persists in the absence of renal ischemia there is usually a secondary decrease of renal blood flow This occurs because of arteriolar constriction affecting both afferent and efferent arterioles The humoral vasoconstrictor which causes this is presumably angiotonin At least angiotonin has such an effect in normal dogs and human beings Whether or not renal vasoconstriction results in renal ischemia depends on the balance struck between increased renal resistance and increased arterial pressure Ultimately as structural lesions advance renal ischemia must occur and places life itself in peril Loss of tissue and of excretory function thus finally prevail while the organic arteriolar disease they depend on probably accelerates the cycle of circulatory dysfunction and pressor activity

The stage in the course of essential hypertension at which the renal pressor factors become significant sustaining and perhaps dominant is not easily estimated. Patients who *die* of hypertension almost always show renal arteriolar sclerosis whereas this lesion is uncommon in normotensives even in advanced age The conclusion that renal arteriolar sclerosis is the genetic factor in hypertension is

a natural one, but its opposite, that hypertension causes renal arteriosclerosis is as justified and much more convincing Evidence consists in the demonstration (1) that experimental renal hypertension due to unilateral renal manipulation leads to arteriolosclerosis in the untouched normal kidney of rats, and (2) that biopsy specimens from patients with hypertension which is disabling but not yet fatal show in 28 per cent no or insignificant vascular disease

TABLE 11 —RENAL FUNCTION IN ARTERIAL HYPERTENSION

	NORMAL	ESSENTIAL HYPERTENSION		
		Early	Establ shed	Mal gna t
Renal blood flow†	1 075	1 153	697	369
Renal plasma flow†	675	630	393	216
Glomerular filtration rate†	128	130	93	61
$Tm_{D\ I}$ mg ‡	49	48	36	21
Arterial pressure (Pm mm Hg)	100	126	154	176
Filtration fraction	0 19	0 20	0 24	0 29
Renal blood flow/Tm_{D-I}	23 8	24 6	19 7	17 00
Glomerular filtration rate/$Tm_{D\ I}$	2 68	2 75	2 66	2 95
Resistance per unit $Tm_{D\ I}$				
Afferent	1 12	1 75	3 75	5 65
Efferent	1 04	0 85	1 38	1 60
Total	2 16	2 85	5 11	7 16

Val es given are representative means The data demonstrate (1) the normal pattern of renal funct on in early hypertens on with only increased afferent resistance to blood flow (2) decreased renal functional status in establ shed essential hypertension and in the mal g nant syndrome w th loss of secretory capacity ($Tm_{D\ I}$) as measured with diodrast® iod ne a gre ter decrease in renal blood flow (evidenced by decrease in the funct on renal blood flow/$Tm_{D\ I}$) and because of efferent arteriolar constriction and increased intraglomerular pressure an increase in the volume of filtrate per un t of res dual secretory capac ty Note also the increased total renal vascular res stance (per un t $Tm_{D\ I}$) as the disease advances or becomes more severe

†In cc /1 73 sq m of body surface

‡In mg /1 73 sq m

and (iii) an additional 25 per cent only mild changes (Castleman and Smithwick) (3) Less conclusive although still weighty is the argument from functional studies which indicate that in many patients the patterns of renal blood flow and function are inconsistent with the presence of significant vascular disease (Table 11) Thus the primacy of renal arteriolosclerosis seems unsupported in most cases

But those who insist on the necessity of primary structural

renal change tend also to retreat from the arterioles to the renal artery and suggest that in many cases an adequate stimulus—entirely analogous to a Goldblatt clamp—is to be found in atheromatous partial occlusion The evidence has been analyzed by Yuile who notes It is apparent that atheromatous plaques in the renal arteries usually associated with severe atherosclerosis in the aorta and elsewhere occur in a high percentage of individuals with essential hypertension However a critical analysis of the evidence would seem to favor the view that these lesions are secondary or incidental to the hypertension rather than causative in all but the few instances in which *renal arteriolar sclerosis* is absent. Thus morphologic evidence of renal vascular disease as the primary stimulus to hypertension is not obtainable *in most cases*

The other avenues of pathogenesis functional rather than morphologic are more difficult to establish because the approach is not as objective as that of histology Further functional concepts have still to fight a two-front war forward into the unknown and, at the rear fending off the traditional demand for easily demonstrable primary structural change The mechanisms by which changes of vasomotor activity qualitatively *normal* but quantitatively hyperactive become fixed at higher levels of supine resting pressure can be only vaguely visualized as a combination of neural neurohumoral endocrine and possibly renal factors As prehypertension passes into early hypertension the only demonstrable renal abnormality is constriction of afferent arterioles Such a state could be entirely a functional disorder due to neurogenic vasomotor imbalances

The pattern of renal blood flow differs from this in the typical case of essential hypertension in which failing adjustment is reflected in retinal arteriolosclerosis cardiothoracic vascular disease and renal injury Absolute reduction of renal blood flow is common and the rate of flow per unit of secretory capacity is usually less than normal secretory and concentrating capacities are diminished

The increase in renal resistance extends to both afferent and efferent vessels The increased afferent resistance responds slowly or very incompletely to high spinal or caudal anesthesia In such patients humoral and structural (arteriolosclerotic) renal factors outbalance the normal autonomy of the renal circulation

Transitional cases have now been observed and studies made in fathers with the one pattern whose sons reveal the other From these it seems likely that the two are phases in the course of the disease The supposition is then made that the persistence of early hypertension may elicit changes in renal blood flow, the result of prolonged vasoconstriction or, more probably, of premature arteriosclerosis which stimulate the renal pressor system into action Thus we visualize the stage of beginning vascular disease as the one at which the renal system becomes operative and the disease self perpetuating

This concept of the pathogenesis of hypertension is necessarily incomplete Certainly the factors which determine the localization of nervous energy in the vascular system eliciting vasomotor hyper responsiveness and those which subsequently determine the onset of hypertension at rest and the course of vascular disease are not included in its scope But it does not do violence to the facts and does offer a framework for further study

II TESTS OF RENAL FUNCTION

Whatever the significance of the renal pressor system may be means for demonstrating and interpreting its action in hypertension are not yet available or are indirect and in large degree inconclusive The clinician who would evaluate the status of the kidneys in a case of hypertension is most concerned with tests of excretory renal function As we have seen the disturbances of these two modes of renal function can be wholly dissociated under selected experimental conditions Still they center in one organ and both

respond to changes in the volume and distribution of blood flow so that, in a disease characterized by vascular injury some association of pressor and excretory functions is to be expected

THE STRUCTURAL AND FUNCTIONAL CHANGES

The renal changes in hypertension seem to develop in merging phases of functional and structural abnormality which finally alter blood flow The stage of early hypertension is characterized by vasoconstriction localized in afferent arteries and arterioles This vasoconstriction commonly balances the increase in arterial pressure so that renal blood flow glomerular filtration rate tubular nutrition and function are quantitatively normal In this phase tests will show that excretory function is completely preserved.

Persistent arterial hypertension in man as in the rat is one presumptive cause of accelerated arteriolar sclerosis At about the time sclerosis begins the activity of the renal pressor system probably begins to add to the existing arteriolar vasoconstriction cardiac augmentation and increased arterial tension in the kidney it causes constriction of the glomerular afferent and efferent arterioles The added afferent constriction tends to decrease glomerular filtration pressure while efferent constriction restores it to and above the normal The paired constrictions increase renal resistance to such a degree that despite increased arterial pressure some decrease of renal blood flow commonly results Were it unaccompanied by any other change decreased blood flow would result in a concurrent decrease in excretory function However the increased intraglomerular pressure of hypertension consequent on efferent arteriolar constriction maintains those aspects of excretory function which depend on filtration, even in the presence of ischemia Filtration rate is sustained by squeezing more water (and its dissolved contents) from less blood. Consequently tests of function which reflect the rate of glomerular filtration often yield normal values until renal injury and ischemia are well advanced, although other

evidences of injury may appear Later, the spread of vascular injury so reduces the mass of renal tissue and blood flow that all tests reveal the defect

The first structural lesions are preglomerular They affect, in order of decreasing frequency and degree the renal artery and its *main branches (in the form of atheroma) the small arteriolar* branches (as sclerosis) and the end arteries (as proliferation), the last in malignant hypertension Most characteristic and widespread in long standing hypertensive disease is the afferent arteriolar sclerosis These arterioles apparently in greater degree than arterioles elsewhere, are subject to accelerated senescence induced by high arterial pressure This change follows the pattern of intimal hyalinization, medial hypertrophy elastic tissue degeneration and in malignant hypertension fibrinoid and necrotic degeneration The glomerulus distal to a lightly damaged arteriole may be normal As its blood supply is first impaired the epithelium may proliferate, when blood flow ceases the capillaries ultimately collapse and sclerose The tubule may undergo simple ischemic atrophy Alternatively occlusion of the afferent arteriole may stimulate formation of collateral arterioles from the afferent and interlobular arteries and they may nourish a tubule whose proximal segment becomes hypertrophic The functional value of the aglomerular tubules thus formed is unknown The simple patchy sclerosis with preservation of normal renal stroma pattern spreads and increases in degree until large numbers of nephrons are destroyed But while renal function is often impaired exceptionally does the course of essential hypertension terminate in uremia

The rapid exudative and necrotic change which characterizes malignant hypertension is accompanied by increased renal vasoconstriction an accelerated rate of tissue loss and an added type of structural injury This is hydronephrotic atrophy due to obstruction of the distal tubules Two factors contribute to it One is the more extensive and exudative character of the glomerular injury

which results in greater proteinuria than is common in the atrophy of essential hypertension. The condensation of this protein in the fluid of poorly functioning distal tubules sometimes permanently obstructs them. The other factor leading to tubular obstruction is due to the proximity of the *macula densa* of the distal convoluted tubule to the afferent arteriole. The lesion of this arteriole in malignant hypertension is necrotic and exudative the exudate surrounds binds and obstructs the tubule even when it does not invade the lumen of the arteriole Elsewhere in the parenchyma the accelerated ischemic atrophy of the malignant phase results in accumulations of macrophages and plasma cells which give the tissue the appearance of an inflammatory exudate These disturb the reticular connective tissue and leave occluding scars of abnormal stroma in their wake

Thus the appearance of the kidney in hypertension may be wholly normal or the parenchyma may be normal with beginning afferent arteriolar and arterial sclerosis or the tubules may be patchily atrophic with more advanced arteriolar disease In malignant hypertension the rate and degree of tissue loss are greater the arteriolar lesions more acute and exudative and the type of renal tissue damage hydronephrotic and almost inflammatory as well as ischemic

SELECTION AND USE OF TESTS TO MEASURE CHANGES

The purpose of a test of renal function is to reflect the character of the renal lesion its intensity and the probability or presence of renal failure The achievement of this objective is dependent on the choice interpretation and repetition of tests.

The nature and technic of tests of renal function have been developed to astonishing levels of accuracy through the efforts of Addis Van Slyke and Smith. However selection still depends on the external conditions of the physician's practice Tests which can be performed using office equipment are (1) measurement of pro-

teinuria, (2) counts of urinary sediment and (3) determinations of urinary concentrating power Where the facilities of clinical chemistry are available, (4) the urea clearance may be added to these as well as (5) the phenolsulfonphthalein test The tests used in office practice will be considered in some detail A clinic which deals with large numbers of hypertensive patients should also have means of determining (6) glomerular filtration rate, effective renal blood flow and tubular secretory capacity Specific indications or the demands of research may call for still other tests

1 *Proteinuria*—Estimates of proteinuria may be qualitative adding a semiquantitative description, or chemically quantitative, The heat acetic method is qualitative and the result semiquantitative since it is recorded as 0 trace or 1 to 4 plus The physician should establish for himself some notion of the approximate concentrations of protein to which the semiquantitative symbols correspond A rough estimate is that trace = 0 5, + = 1, ++ = 3, +++ = 5 and ++++ = 10 Gm of protein per liter of urine The quantitative methods may be approximate, adapted to the physician s office laboratory or unnecessarily exacting The approximate quantitative methods commonly used are that of Esbach which does not require a centrifuge and that of Shevky and Stafford which does The latter (p 367) is more rapid and satisfactory Quantitative measurement is hardly worth the effort if the volume and period of urine collection are unknown The measurement is made with urine samples collected over known periods of several hours (e g 12 hours)

Urinary protein in hypertension usually arises in the kidneys although traces may be due to exudation of pyuria in patients who suffer from inflammation of the lower urinary tract Renal proteinuria may result from ischemic glomerular capillary injury which breaks the double barrier of endothelium and epithelium and permits abnormal passage of plasma protein into tubular fluid Alternatively as the result of tubular ischemia the cells may fail to

reabsorb the small amounts of protein normally present in tubular fluid such proteinuria is tubular A glomerular origin is more likely in hypertension The glomerular injury of which proteinuria is an indication may be functional and due to vasospasm—in which case it is fluctuating sometimes transient as during pressor stimulation —or largely structural the result of preglomerular sclerosis when it is constant, sometimes progressive Sclerosis proceeds to obliteration of the glomerulus so that proteinuria ceases in one tubule to appear in another as its glomerulus begins to be affected. Consequently the proteinuria of hypertension never reaches the levels which are common in glomerulonephritis and eclamprogenic toxemia in which blood flows more or less freely over large groups of severely injured glomerular capillaries A common rate of proteinuria in hypertensives with renal vascular injury is 0 5–1 Gm per 24 hours Values rarely exceeding 5 Gm appear when renal injury is widespread because of malignant hypertension Higher rates suggest the presence of some other disease (glomerulonephritis eclamptogenic toxemia, amyloidosis intercapillary glomerulosclerosis) Qualitatively proteinuria points to renal vascular injury quantitatively it indicates the rate of renal injury when very severe it points to a diagnosis other than essential hypertension

2 *Sediment count*—Study of the crystalline deposits in urine is not of direct interest in cases of hypertension But the organized sediment of urine the red and white blood cells epithelium and casts, has the character of a renal biopsy Its description like that of proteinuria may be semiquantitative or quantitative The semiquantitative examination is made by microscopic inspection in a drop or under a coverglass of the sediment from a centrifuged specimen The description here is in terms of the numbers and type of cells per high power field. This method does not serve for more than rough comparison when urine volume and concentration and the technic of observation vary

A quantitative more painstaking and much more worth while

measure of the sediment is obtained by the method of Addis (p 368) The principle is to collect urine during a timed interval and to determine in this specimen the output of protein and the number of formed elements Fluids are usually restricted during collection for two reasons (1) the test is often done concurrently with measurement of maximal specific gravity, (2) red blood cells and hyaline casts disintegrate in dilute neutral or alkaline specimens but persist in specimens which are hypertonic and acid The urine is acid during most oligurias including that due to fluid restriction

Although as many as 2 000 000 red blood cells per 24 hours

TABLE 12 —COUNTS OF URINARY SEDIMENT IN HEALTHY SUBJECTS (MODIFIED FROM NAERAA)

Author	Red Blood Cells Millions	Leukocytes Plus Epithelial Cells Millions	Casts Thousands
Addis	0–0 4 (0 06)	0 03–1 8 (0 32)	0–4 (1)
Goldring	0–1 5 (0 16)	0 02–3 4 (0 65)	0–9 (0 6)
Naeraa			
Healthy adults	0–1 1 (0 13)	0 01–4 (1 0)	0–9 (2 0)
Aged adults	0–2 3 (0 75)	0 19–2 (0 8)	0–15 (7 0)
Lyttle			
Children	0–0 13 (0 01)	0 01–2 5 (0 3)	0–12 (1)

may occur in the urine of a healthy person the practical upper limit of normal is 500 000 (Table 12) Levels higher than 500 000 suggest the advisability of repeated determinations The red cell count has great value in glomerulonephritis since it reflects the acute exudative activity of glomerular irritation Hematuria alone has less significance in essential hypertension in which increased red cell excretion is the result of preglomerular injury which also causes proteinuria The bursts of hematuria (renal epistaxis) which appear and rapidly subside in certain cases of severe essential or malignant hypertension are exceptions to this rule These presumably are due to acute obliteration of a small artery or arteriole with minor renal infarction They are ominous since they point to acceleration of arteriolar disease

Leukocytes and epithelial cells other than squamous epithelium are counted together since they have much the same size and shape The advent of the phase microscope gives promise of more accurate differentiation of these cells. A count greater than 2 000 000 per 24 hours may be considered abnormal The white cells may arise from irritation anywhere in the urinary tract. The count should therefore be done before or at a reasonable interval after genitourinary instrumentation. Renal origin of leukocytes is suggested by systematic exclusion of other foci and by the presence among them of renal epithelial cells and of cellular casts. The urinary leukocyte count in essential hypertension without urogenital infection is not commonly abnormal It varies with the rate of renal vascular injury and therefore with proteinuria and hematuria. When the injury is severe and rapidly extending and assumes the character of an exudate as in malignant hypertension the urinary sediment may reflect this change Chiefly the count is of most value in drawing attention to associated urologic infection It should be recognized *that chronic pyelonephritis* is not excluded by the absence of pyuria on a single test or even on repeated tests

Cylindruria is abnormal when the number of casts is greater than 10 000 per 24 hours In the presence of other abnormalities of the sediment 5 000 casts per 24 hours may be considered abnormal in most people The cast is formed in the collecting and distal tubules from condensed urinary protein and cells The protein is either of local irritative or of glomerular origin Commonly it is glomerular and cylindruria is associated with proteinuria. Slow injury of one nephron which leaves its neighbors intact such as occurs in hypertension may result in cylindruria which seems out of proportion to the accompanying proteinuria. Cylindruria also depends on the concentrations of urinary solutes (urea electrolytes) the pH and as Oliver suggested a carbohydrate factor similar to chondroitin which seems to be secreted in the collecting and distal tubules

The point of junction of distal convoluted and collecting tubules is narrow Plugs of protein condensed in the distal tubule may be prevented from escaping while similar condensations formed in the collecting tubule appear in the urine as casts Those which do not escape may occlude the tubule and cause hydronephrosis and atrophy Heavy cylindruria suggests that such damage may be occurring Protein precipitates most readily in acid highly concentrated urine Plugging of tubules may be inhibited by providing conditions which result in the formation of a neutral or alkaline urine This result may be obtained by increasing water intake to about 3 L daily and, in the absence of uremia, by administering potassium citrate 15 gr to the drachm (1 Gm per 4 cc) after meals in an amount sufficient to maintain the morning urine neutral to litmus

Casts are the only components of the sediment which are necessarily of renal origin Their association with red and white blood cells points to a renal origin of the whole sediment The presence of coarsely granular and of cellular casts is more indicative of a destructive lesion of the nephron than that of hyaline or finely granular casts When most of the nephrons and collecting tubules which unite into a duct of Bellini (the major duct which opens into the calix) are injured and the stream of urine is slow casts form at this site also These casts are unusually large Their appearance presages renal failure

Addis viewing the sediment count as a form of renal biopsy of much more than merely quantitative value insists that the clinician should do the count However an experienced technician can at least arrive at a better expression of the sediment by this than by any other method One disadvantage lies in the false sense of security a number however specious almost always conveys Improperly performed the count is probably more fallacious than inspection of fresh sediment in morning urine An advantage lies in its providing from one aspect—that of exudation—an insight into

the character of the renal injury and by serial counts of changes in the rate of progress The procedure has not won the wide acceptance it deserves Calculation of the count can be greatly simplified by the use of Hines's nomograph (p 370) or by the method proposed by Addis in his book.

3 *Test of urinary concentration*—The estimation of urinary specific gravity is the oldest quantitative test of renal function and the most easily performed The common practice of measuring specific gravity in casual specimens has also made it one of the least dependable whereas it can be one of the most sensitive indexes of renal injury in hypertension.

The specific gravity of an aqueous solution is a measure of the amount of dissolved substance it contains The ability of the kidneys to form urinary fluid of specific gravity different from that of interstitial fluid that is greater or less than about 1 010 depends on osmotic work done by renal cells which separate these fluids Ability to do this work may be measured by inducing water diuresis and measuring the hypotonicity of the resultant urine (dilution test) or by provoking oliguria due to water deprivation and measuring the increase in urinary specific gravity (concentration test) Estimation of diluting power is less valuable than that of concentrating power partly because the range of dilution (1 010–1 0005) is smaller than the range of concentration (1 010–1 026 or *more*)

Comparison of results of concentration tests shows that the method of water deprivation must be standardized. Of the procedures used the Addis test (p 367) seems the most satisfactory and is also adapted to the simultaneous observations of proteinuria and sediment count. Specific gravity is measured in the urine formed during the last 12 hours of a 24 hour period of fluid deprivation The result is recorded as *maximal urinary nonprotein specific gravity* since correction is made for proteinuria. The lower limit of normal concentration ability is 1 026 rarely 1 025

The function measured by the test is the degree to which urine

The point of junction of distal convoluted and collecting tubules is narrow Plugs of protein condensed in the distal tubule may be prevented from escaping, while similar condensations formed in the collecting tubule appear in the urine as casts Those which do not escape may occlude the tubule and cause hydronephrosis and atrophy Heavy cylindruria suggests that such damage may be occurring Protein precipitates most readily in acid, highly concentrated urine Plugging of tubules may be inhibited by providing conditions which result in the formation of a neutral or alkaline urine This result may be obtained by increasing water intake to about 3 L daily and in the absence of uremia by administering potassium citrate 15 gr to the drachm (1 Gm per 4 cc) after meals in an amount sufficient to maintain the morning urine neutral to litmus

Casts are the only components of the sediment which are necessarily of renal origin Their association with red and white blood cells points to a renal origin of the whole sediment The presence of coarsely granular and of cellular casts is more indicative of a destructive lesion of the nephron than that of hyaline or finely granular casts When most of the nephrons and collecting tubules which unite into a duct of Bellini (the major duct which opens into the calix) are injured and the stream of urine is slow casts form at this site also These casts are unusually large Their appearance presages renal failure

Addis viewing the sediment count as a form of renal biopsy of much more than merely quantitative value insists that the clinician should do the count However an experienced technician can at least arrive at a better expression of the sediment by this than by any other method One disadvantage lies in the false sense of security a number however specious almost always conveys Improperly performed the count is probably more fallacious than inspection of fresh sediment in morning urine An advantage lies in its providing from one aspect—that of exudation—an insight into

its last hours pass during sleep An error in interpretation may arise from the patient's diet, which, as in the rice diet may be abnormally deficient in protein and salt so that those solutes which contribute most to specific gravity urea and salt, are lacking In such

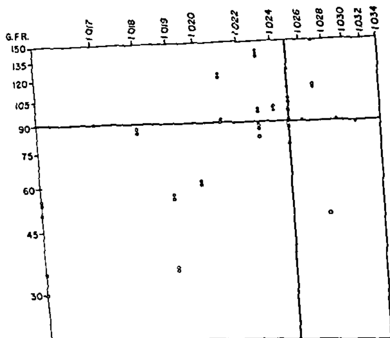


FIG 9—Scattergram of glomerular filtration rates and concurrent maximal urinary concentrating power for 116 patients with essential hypertension 53 in the malignant phase (open circles) The vertical and horizontal bars indicate lower limits of normal for each function. The scatter demonstrates the tendency to lose concentrating power while maintaining normal or nearly normal rates of glomerular filtration

patients as in those who are excessively hydrated the renal cells are not fully stimulated by the routine of the test.

The result of the test should not be interpreted directly in terms of tubular integrity or injury without confirmatory evidence Actu

can be concentrated in the nephron by reabsorption from the isotonic tubular fluid of a hypotonic solution into the blood This final concentration is performed by cells of the distal convoluted tubule A normal result suggests that these cells are intact and normally responsive when the stimulus incited by water lack causes an increase in the osmotic concentration of body fluid and in turn secretion of posterior pituitary hormone which acts on the tubule cells Distal and proximal tubules are commonly injured together by disease The maximal urinary specific gravity therefore usually parallels the more complicated tests of proximal tubular function, such as that of the ability to secrete diodrast* or p aminohippurate The association of decreased concentrating power and tubular secretory capacity like the relation between falling concentrating power and loss of glomeruli persists down to a level of 10–20 per cent of the normal At this point the maximal urinary specific gravity is about 1 010 (hyposthenuria) With further progress of the disease, the ability to dilute is also lost and the urinary specific gravity becomes fixed and the urine isotonic (isosthenuria) The test is therefore to be thought of as a sensitive means of estimating renal function, available to the physician in his office but of no further value once the renal injury has progressed to the onset of renal failure

The test simple in practice has several sources of error which must be considered in its interpretation It is usually contraindicated in the presence of azotemia of any definite degree (e g when blood urea nitrogen is over 25 mg per 100 cc) The stimulus of water lack may be inadequate because the patient mistakenly drinks fluid on the day of the test is excessively hydrated from the day before or is beginning to release edema Performance of the test requires the patient s understanding and co operation and the exclusion of receding edema Those whose ability to concentrate urine is greatly impaired and even those with normal function may be disquieted by thirst despite the use of chewing gum This is avoidable to some degree by starting the period of water deprivation at 8 A M so that

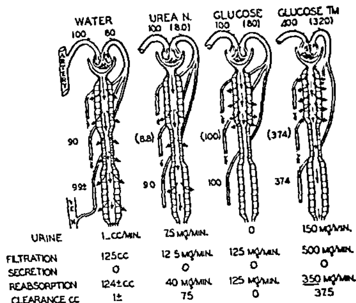


FIG 10—Schematization of excretion of water urea and glucose Each schematic nephron represents the normal renal function of a human being. Numer cal alues opposite blood vessels indicate concentrations, respectively of plasma water urea and glucose Bracketed values are idealized i e., they repre sent concentrations which would obtain were plasma water not filtered with the solutes In the case of water of 100 per cent of renal arterial plasma water 20 per cent is filtered more than half of the filtrate is restored to the plasma by proximal tubular reabsorption and the remainder except the small volume wh ch appears as urine s reabsorbed in the distal tubule. With a filtration rate of 125 cc per minute water reabsorption is 124 cc. per minute when urine olume s 1 cc per m nute The second nephron represents urea clearance when arterial urea N is 10 mg. per 100 cc. of which 20 per cent is filtered a frac t on s reabsorbed and the amount excreted per minute is equivalent to 75 cc. of blood or plasma. In the case of glucose at normal plasma level (100 mg. per 100 cc) 125 mg. is filtered and reabsorbed each minute At high plasma levels (400 mg per 100 cc) the amount filtered s 500 mg. the amount ex reted 150 mg. per m nute the difference (500 minus 150) of 350 mg. per minute represents the maximal glucose reabsorptive capacity of the tubules. This datum is abbrev ated as glucose Tm.

ally, the degree of concentration depends on (*a*) the ability of the renal cells to work and (*b*) the amount of work they are called on to do If, as is common in hypertension the volume of glomerular filtrate presented to the remaining tubules is greater than normal, the concentration of the resultant urine may be low in proportion to the actual renal injury Conversely, when some factor such as congestive failure abnormally depresses formation of glomerular filtrate, tubules really deficient in concentrating power may deliver urine of high specific gravity The concentration test is therefore best interpreted when there is also available a measure of the concurrent rate of glomerular filtration This is most easily obtained from the determination of urea clearance

4 *Urea clearance*—The French word for clearance is *épuration* It conveys the notion of purification of a volume of blood somewhat more clearly than does the word clearance As originally used by Van Slyke the term clearance was applied to urea, it may be extended to any substance which is present in blood and excreted into the urine The concept is used because neither the blood urea concentration nor the rate of urinary urea excretion separately provides an index of the change the kidneys make in the blood which passes through them Thus excretion rate or blood level may be low because of a low protein diet or both be increased by a meat meal Concurrent measurement and comparison of the two excludes factors other than renal in the resulting index Urea clearance by definition is the least volume of blood (or plasma) whose content in urea is equal to the amount of urea excreted in one minute Thus if the urine formed in one minute contains 7 5 mg of urea nitrogen and the blood contains 10 mg of urea nitrogen per 100 cc the least volume of blood which contains 7 5 mg is 75 cc and this volume is the urea clearance Mathematically this volume might represent removal of all the urea from 75 cc of blood or fractional removal from a much larger volume Actually the rate of renal blood flow is about 1 L per minute so that nor

of urea excretion Blood urea is present in solution in plasma and red blood cell water Some 20 per cent of the plasma water with its contained urea is filtered through the glomerular capillaries If filtration rate is 125 cc per minute and blood urea nitrogen 10 mg per 100 cc the amount of urea filtered is 12 5 mg per minute Thus urea clearance if it could be measured at the glomerular exit, would be 125 cc per minute that is equal to the rate of glomerular filtration It is normally less than filtration rate because urea is a small molecule which diffuses rapidly and easily through cell membranes and is thus partly reabsorbed in the renal tubule during reabsorption of water A high rate of urine formation especially as it begins depresses reabsorption and therefore brings urea clearance close to filtration rate Oliguria with slowing of the tubular stream, permits more urea to be reabsorbed so that urea clearance is further reduced from filtration rate At a steady or falling urine flow greater than about 2 cc. per minute most people reabsorb a fairly constant 40 per cent of the filtered urea. Urea clearance is therefore about 75 cc per minute. At a steady urine flow of 1 cc per minute rather more than 50 per cent of filtered urea is reabsorbed and urea clearance averages 55 cc per minute Urea clearance measured at rates of urine flow greater than 2 cc per minute is termed maximal clearance while that measured at lower rates of flow is termed standard clearance Measurements are in either case expressed in percentage of average normal Particularly at higher rates of urine flow which are constant or falling when the patient is at rest and the urine collection complete results of this simple test are remarkably reproducible The range of variation between different people is about 70–140 per cent of normal [1]

Thus urea clearance depends on two processes glomerular filtration and tubular reabsorption Tubular secretion of urea if it occurs in man probably has little significance on the result of the test The precautions taken to stabilize urine flow are intended to obviate variations of tubular reabsorption so that the test will

mal urea clearance of 75 cc represents the extraction by the kidney of about 7 per cent of its urea content Clearance is therefore an ideal or virtual volume (like a virtual image) and not a real volume of blood (Fig 10)

Urea, as the principal end product of protein metabolism, is constantly present in blood, where it may be measured as such or estimated from measurement of nonprotein nitrogen The rate of urea formation depends on the rate of protein metabolism, and this rate is relatively constant from one patient to another Consequently, renal injury with partial failure of urea excretion is commonly associated with an increase in blood urea and nonprotein nitrogen which begins to be evident in most people at about 50 per cent of normal clearance Still protein intake and metabolism vary from person to person and from hour to hour, and the physician who wishes to determine renal function cannot easily take all these factors into account Measurement of serum creatinine yields an index of renal azotemia which is relatively independent of dietary protein intake But this test is also relatively insensitive in early renal impairment. The determination of urea clearance therefore yields information which in the early stages cannot be obtained from determinations of blood urea nonprotein nitrogen or even serum creatinine

Urea clearance (p 372) is one of the most widely used diagnostic procedures because (*a*) urea is normally present in blood and urine and need not be administered (*b*) the methods for its measurement are standardized for performance in the usual clinical laboratory and (*c*) the procedure itself does not demand unusual skills The test requires the collection of two or more specimens of urine over measured intervals of time and a blood sample collected about midway between the urine samples During the collection the patient is at rest Standing and exercise depress filtration rate and urine flow and thus depress clearance

Interpretation of the test requires visualization of the mechanics

of urea excretion Blood urea is present in solution in plasma and red blood cell water Some 20 per cent of the plasma water with its contained urea is filtered through the glomerular capillaries. If filtration rate is 125 cc. per minute and blood urea nitrogen 10 mg per 100 cc the amount of urea filtered is 12 5 mg per minute Thus urea clearance if it could be measured at the glomerular exit, would be 125 cc. per minute that is equal to the rate of glomerular filtration It is normally less than filtration rate be cause urea is a small molecule which diffuses rapidly and easily through cell membranes and is thus partly reabsorbed in the renal tubule during reabsorption of water A high rate of urine forma tion especially as it begins depresses reabsorption and therefore brings urea clearance close to filtration rate Oliguria with slowing of the tubular stream permits more urea to be reabsorbed so that urea clearance is further reduced from filtration rate. At a steady or falling urine flow greater than about 2 cc per minute most peo- ple reabsorb a fairly constant 40 per cent of the filtered urea. Urea clearance is therefore about 75 cc per minute At a steady urine flow of 1 cc per minute rather more than 50 per cent of filtered urea is reabsorbed and urea clearance averages 55 cc. per minute Urea clearance measured at rates of urine flow greater than 2 cc per minute is termed maximal clearance while that measured at lower rates of flow is termed standard clearance Measurements are in either case expressed in percentage of average normal Particularly at higher rates of urine flow which are constant or falling when the patient is at rest and the urine collection complete results of this simple test are remarkably reproducible The range of varia tion between different people is about 70–140 per cent of normal

Thus urea clearance depends on two processes glomerular fil tration and tubular reabsorption Tubular secretion of urea if it occurs in man probably has little significance on the result of the test The precautions taken to stabilize urine flow are intended to obviate variations of tubular reabsorption so that the test will

serve as a measure of the rate of glomerular filtration Variations of urea clearance from the normal are therefore interpreted in terms of glomerular filtration When the number of glomeruli is normal filtration may be depressed by increased renal tissue pressure, *glomerular capillary injury* or a decrease of *hydrostatic filtration* pressure Filtration pressure may be depressed by structural or functional abnormalities of the arterioles and especially by any influence which reduces the lumen of preglomerular vessels Alternatively *decreased filtration may reflect a decreased number* of glomeruli, unlike concentration power this decrease continues as the number of glomeruli decreases to the point where life can no longer be sustained

At the stage in hypertension which we consider functional renal blood flow glomerular filtration rate and tubular function are normal as is the urea clearance When later filtration pressure increases and renal blood flow begins to decrease urea clearance may still be unchanged Renal blood flow is less but proportionately more urea is being filtered The progress of vascular injury reduces the number of glomeruli and the rate of renal blood flow so that urea clearance and filtration rate decrease despite increased filtration pressure A decrease of urea clearance to below normal therefore usually implies widespread renal vascular damage In malignant hypertension in which renal injury is particularly severe and rapid the progress of the disease may be estimated and prognosis guessed by plotting monthly determinations of urea clearance *against time When the power to concentrate urine is lost* the subsequent decreases of urea clearance reflect the further progress of renal injury Urea clearance of about 20 per cent of normal suggests that renal failure is likely and a rate of 10 per cent is usually associated with uremia A low rate of urea clearance may result from a temporary reversible decrease in glomerular filtration such as may occur in heart failure or in the hypotension which temporarily follows myocardial infarction In such cases the urine formed

will usually be small in volume and high in specific gravity Dissociation of urea clearance and concentrating power of this type is therefore frequently an index of extrarenal disability The combined measurement of concentration tests and urea clearance provides the physician s most useful approach to the determination of renal function in hypertension.

The generalization that concentrating power decreases before urea clearance has certain exceptions In some cases, the two tests fail proportionately or clearance is the more affected The pattern of predominantly failing clearance is more common in glomerulonephritis and pyelonephritis than in typical essential hypertension Elderly hypertensive patients whose disease is largely arteriosclerotic, and occasional patients with malignant hypertension will maintain concentrating ability when clearance is significantly decreased Apparently here the reduction of glomerular filtration rate proceeds as rapidly or more rapidly than concurrent tubular damage It may be that the abnormal hypertrophic nephrons which form in the wake of glomerular injury sometimes function in concentration but not in clearance

5 *Filtration rate Renal blood and plasma flow Tubular capacity*—Estimates of the levels of renal blood flow, glomerular filtration rate and tubular secretory capacity have been introduced repeatedly into this discussion of renal injury in hypertension This would have been no more than a presumptuous guess a few years ago The change has been accomplished largely through the efforts of Dr Homer Smith and his colleagues of New York University Their applications of the concept of clearance permit a more complete visualization of renal circulatory and structural function than is available for any other organ

Unfortunately these tests are not widely used Partly this is because they are new partly because they are inconvenient to the physician and uncomfortable to the patient, since catheterization and intravenous infusions are required. The information they yield

seems to us to more than balance these objections Details of specific tests are presented in the Appendix, page 376

a) Glomerular filtration rate Certain substances, notably inulin are characterized by the fact that when injected intravenously they go into solution in the plasma water, are filtered with this water through the glomeruli and are neither added to nor removed from the renal tubular fluid, so that all that was filtered appears in the urine Urinary inulin equals the amount filtered, the amount filtered is the equivalent of 130 cc of plasma. If there is 10 mg of inulin per 100 cc of plasma a normal person will excrete about 13 mg per minute It follows that plasma inulin clearance (the least plasma volume equivalent to one minute s urinary excretion) of 130 cc per minute is also the actual volume of glomerular filtration in cubic centimeters per minute

b) Renal plasma flow Other substances notably diodrast* hippuran* and para aminohippuric acid are excreted in a very different manner In each instance a fraction of that injected is bound to plasma protein, the remainder is in free solution in plasma water, with which it can pass through the glomeruli with the glomerular filtrate The remainder—of diodrast* roughly 85 per cent of that which was present in renal arterial blood—enters the peritubular capillaries and diffuses into the renal interstitial fluid As it comes in contact with the basement membrane of the cells of the proximal convoluted tubule it enters the cell is transferred through it by a physiochemical system which may be visualized as a conveyor belt and is discharged into the tubular fluid Apparently none is reabsorbed Thus the blood which flows on into the renal vein will contain only as much diodrast* as will bring it into equilibrium with renal interstitial fluid Thus with 1 mg of diodrast* (measured in terms of its iodine content) per 100 cc of plasma a small amount—roughly 0 15 mg per 100 cc—is filtered the remainder is secreted through the tubules and a trace remains in the distal tubular plexus The urine of a normal person will in this

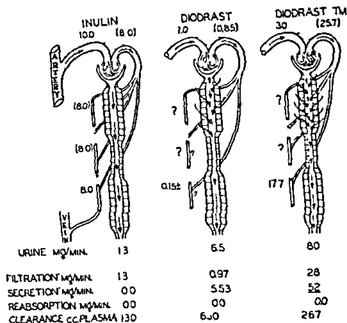


FIG. 11 —Schematization of inulin and diodrast* clearance and of measurement of tubular secretory capacity for diodrast* (diodrast* Tm) In the case of inulin 10 mg is assumed to be present in 100 cc. of renal arterial plasma 2 mg. is filtered from each 100 cc of plasma, leaving the equivalent of 8 mg. per 100 cc in efferent arteriolar and peritubular plasma none is reabsorbed but nearly all the filtered water is restored leaving the concentration of inulin at 8 mg. per 100 cc in renal venous plasma. One minute's urine contains 13 mg. of *inulin this is the equivalent of* 130 cc. of renal arterial plasma the renal plasma clearance of inulin is thus 130 cc. per minute The schematization in the case of diodrast at low plasma levels is similar In the case of diodrast* Tm a renal arterial plasma concentration of 30 mg. per 100 cc. is assumed Knowledge of glomerular filtration rate plasma diodrast* concentration and plasma protein levels yields the datum that 28 mg. of diodrast* appears in the urine as the result of filtration the urinary diodrast* excretion equals 80 mg. per minute the difference (80 minus 28) is 52 mg. per minute This value represents the maximal secretory capacity of the tubules for diodrast.* Diodrast* values are expressed as milligrams of diodrast* iodine

Inulin and thiosulfate (S_2O_3) are excreted in an identical manner and para aminohippurate (PAH) and diodrast* also correspond. Mannitol is subject to slight reabsorption and cannot quite be used interchangeably with inulin Apparent mannitol reabsorption is about 10 per cent. *The numerical detail of the* third (Tm) figure would require slight changes if PAH were substituted for diodrast* principally because the mean normal tubular secretory capacity for PAH (Tm_{PAH}) is about 80 mg per minute

example, contain about 6 5 mg of diodrast® per minute Diodrast® clearance is therefore 650 cc of plasma But since the renal re moval of diodrast® is nearly complete, the clearance volume is not ideal or virtual as is urea clearance but is nearly real and nearly equal to the volume of plasma which flowed through the kidney during the time clearance was measured The actual volume of plasma which comes into contact with functioning renal tissue is therefore 650–700 cc, the equivalent of 1 000–1 200 cc of whole blood (Fig 11)

c) Secretory and reabsorptive capacity The plasma concentra tion of a secretable substance such as diodrast® may be increased to such a level that the amount carried to the kidneys is greater than the discharge capacity of the secretory system That part which the cells cannot transfer remains in interstitial fluid and equilibrates with the renal venous blood Renal extraction falls and plasma clearance becomes less than the actual volume of renal plasma flow In the example (Fig 11) measurement of urinary diodrast® indi cates an excretion rate of 80 mg per minute Concurrent measure ment of glomerular filtration rate indicates that 28 of the 80 mg was filtered The remainder 52 mg per minute is the maximal ca pacity of the secretory system The measurement of secretory capac ity provides a specific index of one tubular activity

Reabsorptive function may be measured in an analogous man ner In the case of glucose at low plasma levels, all that is present in the glomerular filtrate is reabsorbed by the tubules This reab sorption occurs through the action of a transfer system which car ries glucose from tubular lumen to cellular basement membrane whence it enters interstitial fluid and ultimately re enters the blood Its path is the reverse of that followed by diodrast® If the plasma glucose concentration is increased the amount of glucose filtered (plasma concentration × filtration rate) may exceed reabsorptive capacity Glycosuria results The difference between the amount of glucose filtered and the amount excreted (usually about 350 mg

per minute) is the reabsorptive capacity of this tubular system (Fig 10 p 275)

The concepts we have presented of renal blood flow and function in hypertension depend largely on the application of these tests Their present restricted use does not seem to justify elaborate description of our results Detailed discussions are provided by Smith and by Goldring and Chasis They have observed that patients with essential hypertension may show depression of tubular secretory capacity while filtration rate and ability to reabsorb glucose are unimpaired The mechanism of this dissociation of function is unknown although it serves as an example of the detail with which renal function may now be visualized. The significance of these tests seems to us to lie in the fact that they provide measures of renal blood and plasma flow of glomerular filtration rate and tubular function from which estimates can be made of the character and extent of renal vasoconstriction and injury in the course of the disease These estimates serve as background on which the results of simpler tests may be visualized during their routine application

III RENAL FAILURE

The probability that accelerated arteriolar senescence of hypertension will progress to a fatal defect of excretory function may be suggested by the complaint of nocturia the appearance of anemia or better estimated from successive tests of excretory function No other clues fill the gap between the least and the last degrees of renal injury In the interval the residue of renal function is ordinarily sufficient to maintain the composition of the body fluids at levels consistent with well being Indeed so characteristic is renal arteriolar sclerosis in hypertension that progress toward renal failure is inexorable unless the disease can be radically altered by treatment or as is more common cut short by an extrarenal cause

The loss of renal parenchyma in hypertension is the result (1)

of restriction of blood flow, functional and structural, and (2) of interstitial exudate and fibrosis to which may be added (3) tubular obstruction, either extrinsic from exudate around necrotizing arterioles or intrinsic due to proteinuria (p 269) The first acts almost alone in essential hypertension and usually at a slow pace. In contrast, it is much more severe in malignant hypertension in which the second and third processes also become conspicuous This summation of factors speeds the onset of renal failure so that death occurs from this cause in about 60 per cent of hypertensive patients who develop the malignant syndrome and in only about 5 per cent of those who do not In fact renal failure in essential hypertension is all but limited to a few whom fortune has preserved from fatal cardiac or cerebral injury until they are overtaken by it at about age 65

A disproportionate interest in the renal structural lesions with only passing consideration of clinical course and associated sys

---

FIG 12—Photomicrograph of a small sprig from Neoprene cast of a normal kidney including terminal interlobular arterioles glomerular arterioles glomeruli and in many places the intertubular capillary plexus. The arteries show a smooth contour with regular and gradual diminution of caliber afferent arterioles come off at regular intervals and in about normal abundance with practically no spurs on the arteries to represent occluded afferent arterioles The white balls represent fully injected tufts of glomerular capillaries the threadlike networks especially at the periphery are intertubular capillary plexuses Both kidneys appeared grossly normal the opposite kidney was also normal microscopically

FIG 13—In contrast to the normal specimen this cast of a nephrosclerotic kidney shows slight and rather inconspicuous irregularity in contours of the interlobular arteries especially near their terminations Most striking are the reduction in total number of glomeruli injected the irregularity and general smallness of their size and the long stretches of artery in which the former sites of glomeruli are represented only by small spurs believed to be remnants of obstructed arterioles The net result is the blighted tree appearance. This cast was made from the kidney of a man 60 with hypertensive and coronary heart disease who died of progressive myocardial failure Both kidneys appeared alike in the gross the opposite one showed gross and microscopic pictures of moderate arteriolar nephrosclerosis (Courtesy of Dr G Lyman Duff and Dr R H More Pathological Institute McGill University Montreal)

FIG. 12 (*above*) FIG. 13 (*below*) Legends on p. 284

temic vascular lesions gave rise to the concept of nephrosclerosis, benign and malignant The former corresponds to essential hypertension with some degree of renal injury, the latter to the syndrome of malignant hypertension The artificiality of the concept can be illustrated by supposing that patients who die of coronary or cerebral arterial disease could be adequately described as suffering from coronary or cerebral vascular sclerosis A similar even more misleading limitation is implied by the concept of chronic interstitial nephritis for nephritis carries the connotation of infection in fact the background of this concept rests in an attempt to link glomerulonephritis and hypertension Confusion of thought is best avoided by dropping the compound diagnosis of hypertension with interstitial nephritis Actually the association of essential hypertension with glomerulonephritis is rare and probably undiagnosable

UREMIA

Uremia is the clinical syndrome which marks the point at which renal insufficiency has advanced enough to alter the composition of body fluids with resultant serious disturbance of bodily functions

The precise cause of the syndrome remains obscure although it may be assumed to arise from retention of substances the normal kidney excretes or alters One of these urea gave the name, for its accumulation in blood was mistakenly assumed to cause the characteristic illness Actually no one of the chemically defined constituents of blood can be directly implicated The irregularity of its onset in relation to the concentration of substances in the blood may reflect individual tolerance to change in body fluids The classic syndrome seems to depend on the loss of large areas of renal parenchyma in addition to excretory failure

Diagnosis—The diagnosis of uremia is thus clinical and cumulative rather than dependent on any single observation It is made from (1) the nature of the preceding and attendant illness (2)

the clinical symptoms and signs and (3) the demonstration of a great degree of renal parenchymal loss

1 The precipitating illness As we have seen malignant hyper tension commonly results in uremia whereas in uncomplicated es sential hypertension uremia is rare The presence of malignant hypertension may be established from the history and physical ex amination its distinction from terminal glomerulonephritis is made by the history renal findings and the greater degree of cardioaortic and cerebral disease Conversely the diagnosis of glomerulonephri tis is suggested by intense defects of excretory function (p 76) Definition of the nature of the lesion is important, since this may significantly influence the duration and character of the uremic state Thus, the uremia of malignant hypertension is stormy brief and accompanied by cardiac and cerebral injury while that of glomerulonephritis may be prolonged for months and complicated by remediable acidosis and hypochloremia.

Knowledge of the preceding illness will also aid in excluding the acute and pseudouremias of acute nephritis, eclampsia and hypertensive encephalopathy These forms of cerebral disturbance have nothing in common with true uremia. Since they are usually easily distinguished from it, the term uremia should not be applied to them.

2 Symptoms and signs Because it is not complicated by severe extrarenal disease the classic and characteristic form of uremia is that which slowly supervenes in essential hypertension or in ter minal glomerulonephritis Here the onset is insidious Most of the symptoms arise in disturbances of central nervous system function The sequence begins with weakness and anemia. Later anorexia leads to loss of weight and progresses to nausea at the sight of food and vomiting after eating Headache appears or is intensified and extended through the 24 hours Dulness and apathy alter the per sonality Vertigo may be distressing Depression commonly ad vances into coma but may be replaced by toxic delirium at first oc

casional and nocturnal and later persistent In a few patients, a toxic psychosis with organized paranoid or melancholic trends appears (folie brightique) Recognition of the time of onset and the nature of the change in consciousness is important since the patient s testamentary capacity may be influenced Generalized motor convulsions are rare at the onset but common in later stages when they punctuate periods of stupor Pruritus may be an early sign Food and drug (e g morphine) sensitivities may newly appear and cause distressing urticaria

The final stage is one of deepening coma, vomiting muscular twitching and incompletely organized convulsions The breath is foul it is ammoniacal because oral bacteria decompose the salivary urea and form ammonia The tongue is coated and dry Gastrointestinal disturbance is further marked by stomatitis and colitis with diarrhea Hemorrhagic diathesis with epistaxis subcutaneous hemorrhages and melena is common The scratch marred skin is inelastic due to dehydration Dyspnea of the air hunger type may appear as the result of acidosis Terminally a frost of urea crystals forms over the shoulders and chest when azotemia is intense Pericarditis, usually painless and marked by a friction rub precedes death by a few weeks at most

This typical pattern is modified by the associated hypertensive state The uremia of hypertension assumes three forms One the uncommon form of late essential hypertension runs a prolonged course of several months such as is described above Acidosis and hypochloremia may significantly complicate the disease and their relief will do much to increase comfort and prolong life The slow accumulation of nitrogenous residues results in extreme heights of azotemia and anemia may be very severe

The commonest form is that which closes the malignant phase The onset is often sudden extending over a few days The course is rapid being completed in one to three weeks Azotemia is not intense acidosis and hypochloremia are usually insignificant This

attern of renal failure is associated with severe cardioaortic and erebrovascular disease In such patients renal excretory failure is not as severe at the onset of disability as it is in those whose uremia is not combined with other factors (p 76)

In certain patients with severe essential hypertension many of the symptoms of uremia appear in association with congestive heart failure The degree of renal parenchymal loss may be less than that commonly associated with classic uremia and the progress such that it seems likely that heart failure is a proximate cause of the excretory deficit. The preponderance of the cardiac element is indicated by the excretion of a small volume of urine whose specific gravity is greater than 1 012 Relief of heart failure temporarily abates the condition

3 Loss of renal parenchyma This is indicated by changes in blood and urine Urinary specific gravity is fixed regardless of urinary volume at about 1 010 Proteinuria may be very slight The bulky casts of renal failure appear in the sediment.

There is *azotemia* measured as increased nonprotein or urea nitrogen Creatinine and guanidine are present in the blood in increased amounts as are substances measured as phenols Carrying out the error which first attributed uremia to accumulation of urea it is sometimes taught that uremia may be diagnosed from some set level of azotemia. Actually the degree of azotemia at which uremia begins varies widely and is highest in patients whose renal failure is the result of slowly progressive disease Diet and infection are two of the most important determinants of the level of azotemia. However since there must be considerable impairment of excretion for uremia to develop some degree of azotemia is necessarily present Roughly this lower limit of uremic azotemia may be set at about 60 mg of urea nitrogen and 90 mg of nonprotein nitrogen per 100 cc of blood

Determinations of *clearance* reveal severe functional loss with the level of urea clearance less than 10 per cent of normal

Prolongation of renal failure permits the appearance of the sec ondary remediable changes of acidosis and hypochloremia Al though significant in chronic glomerulonephritis, they are not im portant complications of the uremia of malignant hypertension Acidosis results from retention of acid ions principally phosphate and sulfate together with increased urinary loss of sodium the latter partly because the injured kidney cannot form ammonia Clinically acidosis is indicated by air hunger and confirmed by a low level of plasma carbon dioxide content or combining power Inability to prevent loss of sodium involves loss of chloride Dep rivation of sodium and chloride results in a decrease of plasma and interstitial fluid volumes and of plasma chloride, sodium and total base Thus there is added to the discomfort of dehydration a decreased glomerular filtration rate due to oligemia which intensi fies or may unnecessarily precipitate uremia Hypochloremia also increases anorexia, vomiting and depression and in uremia is often associated with potassium retention with resultant muscle twitches and electrocardiographic changes The latter, carried to the extreme ends in cardiac arrest

Management—Because of the grave prognosis the object of treatment is somewhat different from that in earlier stages of hyper tension It is first to make life comfortable and not intolerable and second to remedy defects in body metabolism such as hypochlo remia and acidosis as they appear Occasionally metabolic defects are caused or accentuated by misguided treatment It is as important not to do certain things as it is to do certain others

With the onset of uremia reorientation in the social relation ships of the patient is desirable Means should be provided to pur chase the small comforts and satisfy the simple personal desires of the patient Rest in bed need be recommended only as it is desired Hospitalization is necessary only as special needs arise and the visit should be made as brief as consistent with the patient s comfort Responsible relatives must be informed of the outlook and the

purposes underlying the treatment. In brief we consider it a therapeutic achievement when the patient *walks* into the hospital and when his stay there is brief Despite the serious metabolic disorder of uremia life has been made bearable if not enjoyable and the agonies of prolonged uremia have been avoided

Failing appetite often precludes the administration of any special diet Diets low in protein but adequate in calories have been shown to protect against both azotemia and uremia Such are the low protein regime of Addis (about 0 5 Gm protein per kilogram body weight daily) and modifications of the rice diet of Kempner It is especially important to maintain an adequate volume of urine of about 2 L. daily Protein free diets of sugar and butter are useful in severe situations (Borst) and most important is control of active or latent infection A few patients seem to have better appetites when vitamin B complex is administered. Since salt may be lost in large quantities owing to inability to concentrate urine too severe restriction of sodium may lead to the syndrome known as hypochloremic uremia. If this is suspected determination of the serum chloride content will give the answer

The administration of large amounts of salt must sometimes be avoided because of the usual imminence of cardiac failure A compromise must be reached in which not enough salt is given to aggravate the edema of cardiac failure but sufficient is allowed to prevent hypochloremia In most patients 3–5 Gm suffices If salt is administered without equivalent amounts of water the salt is retained For this reason, ingestion of salt must be accompanied by enough fluid to insure adequate urine flow

Similarly a few patients show excessive urinary losses of potassium with resultant weakness and electrocardiographic change *As long as urine flow is abundant* the potassium deficit can be repaired by oral potassium chloride or citrate (2–4 Gm daily)

The retention chiefly of acids loss of base by vomiting and the decreased formation of ammonia by the kidneys lead to acidosis It

increases the nausea and vomiting of uremia By addition of the dyspnea of acidosis, distress is increased

Acidosis is treated by intravenous or, when tolerated, by oral administration of alkalinizing salts Two conveniently available are sodium bicarbonate and sodium lactate Bicarbonate is given orally in a dose of 0 026 Gm per kilogram of body weight for each 1 volume per cent deficit from the normal of serum carbon dioxide combining power It may be given intravenously The dry bicarbonate is weighed into paper sacks and heat sterilized, the sterile bicarbonate is added to sterile water (13 Gm per liter) and infused The dose of the 1 3 per cent solution is 2 cc per kilogram (9 cc per 10 lb) of body weight per volume per cent deficit in carbon dioxide combining power Alternatively 1/6 molar sodium lactate solution is commercially available The dose is 1 86 cc per kilogram (8 5 cc per 10 lb) of body weight per volume per cent deficit in carbon dioxide combining power Neither substance should be given in a hit or miss manner The persistence of the therapeutic effect should be checked clinically and by repeated determinations of carbon dioxide combining power An adequate oral or intravenous maintenance dose will thus be found

The precipitation or complication of uremia by heart failure is treated by the standard methods (pp 210 ff) There is no evidence that renal insufficiency markedly decreases the maintenance dose of digitalis However care should be exercised in the period of digitalization when toxic manifestations may complicate rapid digitalization It is doubtful that mercurial diuretics have any real place In the presence of renal failure they may be ineffective or if effective may only cause serious electrolyte deficit

Iron is useful in the treatment of the anemia of terminal nephritis only when chronic hemorrhage is occurring It must be given with caution because it may do more harm than good by upsetting the patient s stomach

It is well to prepare for convulsions during the final stage by

warning relatives or nurses of their possibility and having available tongue depressors well wrapped in gauze to prevent injury to the tongue when they occur Hypertonic glucose (50 per cent) given intravenously tends to lessen their frequency and severity If they continue and cause great distress sodium pentobarbital (3 gr) may be given intravenously

One of the most distressing symptoms of uremia is intense itching Unless it is reduced or abolished the patient is miserable We use pine tar ointment (U S P) Obtundia cream applied freely to the skin and ergotamine (1 mg 1/60 gr) orally three times a day

Nausea and vomiting are among the most difficult symptoms to treat. They tend to be less severe if the electrolyte pattern of the blood is kept as normal as possible Glucose given by vein aids greatly in preventing them. Moderate exercise and fresh air reduce th m Some patients find sucking cracked ice soothing Bismuth subnitrate (0 65 Gm) plus sodium bicarbonate (1 3 Gm) may aid A useful procedure to aid in overcoming nausea is to insert into the rectum a capsule of sodium amytal* well lubricated and punched full of holes with the point of scissors

The mouth should be kept clean with any pleasant antiseptic solution and the lips should be well greased with cold cream.

It distresses the patient to be told how pale he looks True the pallor often is ghastly To try to overcome this as much as possible by daily treatment with direct sunlight or irradiation from an ultra violet lamp certainly bolsters the patient s morale

It is often possible and certainly desirable by careful therapeutics to allow the patient normal social contacts and duties until within days or weeks of the final uremic coma or cardiac failure If this is accomplished the physician has done well

BIBLIOGRAPHY

ADDIS T A clinical classification of Bright s disease J A. M. A. 85 163 1925
——— Glomerular Nephritis Diagnosis and Treatment (New York The Macmillan Company 1948)

increases the nausea and vomiting of uremia By addition of the dyspnea of acidosis, distress is increased

Acidosis is treated by intravenous or, when tolerated, by oral administration of alkalinizing salts Two conveniently available are sodium bicarbonate and sodium lactate Bicarbonate is given orally in a dose of 0 026 Gm per kilogram of body weight for each 1 volume per cent deficit from the normal of serum carbon dioxide-combining power It may be given intravenously The dry bicarbonate is weighed into paper sacks and heat sterilized, the sterile bicarbonate is added to sterile water (13 Gm per liter) and infused The dose of the 1 3 per cent solution is 2 cc per kilogram (9 cc per 10 lb) of body weight per volume per cent deficit in carbon dioxide combining power Alternatively, 1/6 molar sodium lactate solution is commercially available The dose is 1 86 cc per kilogram (8 5 cc per 10 lb) of body weight per volume per cent deficit in carbon dioxide combining power Neither substance should be given in a hit or miss manner The persistence of the therapeutic effect should be checked clinically and by repeated determinations of carbon dioxide combining power An adequate oral or intravenous maintenance dose will thus be found

The precipitation or complication of uremia by heart failure is treated by the standard methods (pp 210 ff) There is no evidence that renal insufficiency markedly decreases the maintenance dose of digitalis However care should be exercised in the period of digitalization when toxic manifestations may complicate rapid digitalization It is doubtful that mercurial diuretics have any real place In the presence of renal failure, they may be ineffective or, if effective may only cause serious electrolyte deficit

Iron is useful in the treatment of the anemia of terminal nephritis only when chronic hemorrhage is occurring It must be given with caution because it may do more harm than good by upsetting the patient s stomach

It is well to prepare for convulsions during the final stage by

——— The physiology of the renal circulation, Harvey Lect. 35 116 1939-40
——— Lectures on the Kidney (Lawrence Kan University of Kansas, 1943)
STEINITZ, K. Renal blood flow in healthy persons and in patients with hypertension and renal diseases Acta med Scandinav 109 95 1941
TALBOT J H CASTLEMAN B SMITHWICK, R. H. MELVILLE, R. S., AND PECORA, L. J Renal biopsy studies with renal clearance observations in hypertensive patients treated by radical sympathectomy J Clin. Investigation 22 387 1943
TRUETA J et al Studies of the Renal Circulation (Springfield Ill Charles C Thomas, Publisher 1947)
WILSON C. AND BYROM J B The vicious circle in chronic Bright's disease Quart. J Med 10 65 1941
YUILE, C. L. Obstructive lesions in the main renal artery in relation to hypertension Am. J M. Sc. 207 394 1944

——— A number of formed elements in the urinary sediments of normal individuals J Clin Investigation 2 409 1926
——— AND SHEVKY M C A test of the capacity of the kidney to produce urine of high specific gravity Arch Int Med 30 559 1932
ALVING A S AND VAN SLYKE D D The significance of concentration and dilution tests in Bright's disease J Clin. Investigation 13 969 1934
BORST J G G Protein katabolism in uraemia Lancet 1 824 1948
BRAUN MENENDEZ E FASCIOLO J C LELOIR L F MUÑOZ J M AND TAQUINI A C Hipertension arterial nefrogena (Buenos Aires El Ateneo 1943)
CASTLEMAN B AND SMITHWICK R H The relation of vascular disease to the hypertensive state J A M A. 121 1256 1943
CORCORAN A C AND PAGE I H Renal blood flow in experimental renal hypertension Am J Physiol 135 361 1942
——— TAYLOR R D SHRADER, J C YOUNG W C AND PAGE, I H Correlation of clinical types with renal function in arterial hypertension Proc. Cent Soc Clin Res 15 72 1942
DOCK W Proteinuria and the associated renal disease New England J Med 227 633 1942
FISHBERG A Hypertension and Nephritis (4th ed Philadelphia Lea & Febiger 1939)
FOA P P WOODS W W PEET M M AND FOA N L Effective renal blood flow glomerular filtration rate and tubular excretory mass in arterial hypertension Arch Int Med 71 357 1943
FRIEDMAN M SELZER A AND ROSENBLUM H The renal blood flow in hypertension J A M A 117 92 1941
GOLDRING W AND CHASIS H Hypertension and Hypertensive Disease (New York Commonwealth Fund 1944)
HARRISON T R AND MASON M F The pathogenesis of the uremic syndrome Medicine 16 1 1937
HIGGINS C C Renal Lithiasis (Springfield Ill Charles C Thomas Publisher 1943)
HINES D C A nomograph for simplifying computation of the urine sediment count (Addis) Am J M Sc 187 831 1934
KOHLSTAEDT K G AND PAGE I H The liberation of renin by perfusion of kidneys following reduction of pulse pressure J Exper Med 72 201 1940
LEWIS H A AND GOLDBLATT H Studies on experimental hypertension XVIII Experimental observations on the humoral mechanism of hypertension Bull New York Acad Med 18 459 1942
MASSON G CORCORAN A C AND PAGE I H Dietary and hormonal influences in experimental uremia J Lab & Clin Med 34 925 1949
NAERAA A Studies on urinary sediment I Technique Acta med Scandinav 95 341 1938
——— II Normal counts ibid 95 351 1938
PAGE I H The management of Bright's disease J Indiana M A 33 337 1940
——— AND CORCORAN A C Hypertension A review in Steele J M (ed) Advances in Internal Medicine (New York Interscience Publishers Inc 1942)
PRICE J W MILLER M AND HAYMAN J M JR The relation of specific gravity to composition and total solids in normal human urine J Clin Investigation 19 537 1940
SMITH H W The Physiology of the Kidney (New York Oxford University Press 1937)

——— The physiology of the renal circulation, Harvey Lect. 35 116 1939-40
——— Lectures on the Kidney (Lawrence Kan. University of Kansas 1943)
STEINITZ, K. Renal blood flow in healthy persons and in patients with hypertension and renal diseases, Acta med. Scand nav 109 95 1941
TALBOT J H CASTLEMAN B SMITHWICK, R. H. MELVILLE, R. S AND PECORA L. J Renal biopsy studies with renal clearance observations in hypertensive patients treated by radical sympathectomy J Clin. Investigation 22 387 1943
TRUETA, J *et al* Studies of the Renal Circulation (Springfield Ill. Charles C Thomas, Publisher 1947)
WILSON C., AND BYROM J B *The vicious circle in chronic Bright's disease* Quart. J Med. 10 65 1941
YUILE, C. L. Obstructive lesions in the main renal artery in relation to hypertension, *Am. J M Sc.* 207 394 1944

13 Hypertension and Pregnancy

THE AGE OF childbearing overlaps the lower margin of the age period during which established essential hypertension is common Primary renal hypertension is uncommon enough not to be a serious problem in maternal statistics Therefore were there no other factors hypertension would be only an incidental complication of pregnancy The principal disturbing factor is vascular toxemia of pregnancy, known as eclamptogenic toxemia or pre eclampsia and eclampsia No consideration of this topic is possible without some comment on classifications of hypertension during pregnancy Most of them have the defects inherent in compromises The system proposed by the American Committee on Maternal Welfare reproduced here is by far the most practical Its rigorous use should contribute much to an understanding of this topic Further it is a classification which in revision will demand little more than omission of certain elements such as nephrosclerosis and possibly nephrosis rather than the introduction of new classes

CLASSIFICATION OF THE TOXEMIAS OF PREGNANCY

Group A Disease not peculiar to pregnancy

I Hypertensive disease (hypertensive cardiovascular disease)
   a) Benign (essential) mild severe
   b) Malignant

II Renal disease
   a) Chronic vascular nephritis or nephrosclerosis

b) Glomerulonephritis
(1) Acute
(2) Chronic
c) Nephrosis
(1) Acute
(2) Chronic
d) Other forms of severe renal disease

Group B Disease dependent on or peculiar to pregnancy
I Pre eclampsia
a) Mild
b) Severe
II. Eclampsia
a) Convulsive
b) Nonconvulsive (i e coma with findings at autopsy typical of eclampsia)

Group C Vomiting of pregnancy

Group D Unclassified toxemias

The classification deals with two major groups of cases in which pregnancy and hypertension are associated group A hyper tensive states not peculiar to pregnancy and group B syndromes dependent on pregnancy namely pre eclampsia and eclampsia Alternatively the syndrome dependent on pregnancy may be super imposed on prepregnant hypertension

Essential hypertension or prehypertension present before the end of the fourth lunar month of pregnancy may be modified in one of three ways by the processes of gestation (1) In about half the cases it is unchanged or is modified only by the physiologic pattern of pregnancy (2) In a third or more of hypertensive pa tients the blood pressure may decrease sometimes nearly to normal levels usually between the eighth and the thirty second week the prepregnant arterial tension is resumed It is important not to mis take the rise in tension during the last months for pre-eclamptic toxemia Nevertheless a rise in pressure should be carefully studied since (3) about a third of hypertensive patients develop pre eclampsia or eclampsia usually after the sixth month

1 Those whose hypertensive state is not notably altered may still cause the clinician concern because of edema That the retention of water and salt is an important characteristic of normal pregnancy is not generally appreciated A normal pregnant woman thus gains more weight, especially during the last trimester, than can be accounted for by the products of conception The excess of water and salt is lost soon after delivery This retention probably depends on the stimulation of renal reabsorption of sodium by placental progestational and estrogenic hormones In some 60 per cent of women, whether because of hormonal excess, renal hypersensitivity to salt retaining stimuli or a high salt intake the retention is sufficient to cause edema elsewhere than in the feet and legs

The characteristics of gestational edema have been emphasized by Dexter and Weiss who point out that except in the feet and legs it is nonpitting and does not enter the serous cavities Headache, vomiting and scotomas may appear when the edema extends to the face and head The syndrome is no more common in hypertensives than among normotensives It is diagnostically important especially when there is pre existing hypertension, because the status then resembles eclamptogenic toxemia in which also occur edema headache scotomas vomiting and increased arterial pressure The observations of Dexter and Weiss suggest that water retention predisposes to eclamptogenic toxemia The edema and the symptoms to which it gives rise can be controlled by methods which cause sodium loss namely administration of a low sodium diet and of potassium (chloride citrate nitrate) or ammonium salts (chloride nitrate) in doses of 1 Gm (15 gr) three times a day for three or four consecutive days per week and the drinking of large volumes of water (3–4 L daily)

2 The patients whose prepregnant hypertension seems to be lessened during pregnancy are of interest because a somewhat similar decrease of arterial pressure is regularly observed during pregnancy or pseudopregnancy in animals with experimental renal hy

pertension. It seems probable that this fall in arterial pressure is partly the result of decreased peripheral resistance this decrease is due to the placental vessels acting as low resistance arteriovenous shunts In dogs and apparently in human beings as these vessels sclerose and uterine tone increases in the last weeks of pregnancy the shunt may be lessened and peripheral resistance and arterial pressure again rise Another explanation may be in the marked changes of blood enzymes in pregnancy some of which such as angiotonase may be antipressor

5 Patients in whom eclamptogenic toxemia is superimposed on essential hypertension are of particular importance both diagnostically and prognostically Their consideration depends on a definition of the processes and treatment of pre-eclampsia and eclampsia. The superimposition of pre eclampsia on existing essential hypertension renders the prognosis more unfavorable for both mother and baby than either disease alone and usually calls for prompt termination of pregnancy

Eclamptogenic Toxemia Pre Eclampsia and Eclampsia

Mild degrees of eclamptogenic toxemia can be mistaken for excessive water retention in nontoxemic pregnancy or for prepregnant essential hypertension In toxemia edema is commonly associated with headache vomiting and scotomas The onset may thus be estimated from the symptomatology and a graphic record of body weight which shows a sudden upturn toward the last trimester Arterial hypertension is usual the retinal arterioles show segmental constriction the retina is very often edematous but retinal hemorrhages are uncommon In a nosologic utopia toxemia like measles would be characterized by a specific rash and diagnosis would be as easy Actually this desideratum is partly met, although the rash, hidden in the glomeruli manifests itself as proteinuria. It is doubtful if eclamptogenic toxemia ever arises without pro-

1 Those whose hypertensive state is not notably altered may still cause the clinician concern because of edema That the retention of water and salt is an important characteristic of normal pregnancy is not generally appreciated A normal pregnant woman thus gains more weight, especially during the last trimester, than can be accounted for by the products of conception The excess of water and salt is lost soon after delivery This retention probably depends on the stimulation of renal reabsorption of sodium by placental progestational and estrogenic hormones In some 60 per cent of women whether because of hormonal excess, renal hypersensitivity to salt retaining stimuli or a high salt intake the retention is sufficient to cause edema elsewhere than in the feet and legs

The characteristics of gestational edema have been emphasized by Dexter and Weiss who point out that except in the feet and legs it is nonpitting and does not enter the serous cavities Headache, vomiting and scotomas may appear when the edema extends to the face and head The syndrome is no more common in hypertensives than among normotensives It is diagnostically important, especially when there is pre existing hypertension because the status then resembles eclamptogenic toxemia in which also occur edema headache, scotomas vomiting and increased arterial pressure The observations of Dexter and Weiss suggest that water retention predisposes to eclamptogenic toxemia The edema and the symptoms to which it gives rise can be controlled by methods which cause sodium loss namely administration of a low sodium diet and of potassium (chloride citrate nitrate) or ammonium salts (chloride nitrate) in doses of 1 Gm (15 gr) three times a day for three or four consecutive days per week and the drinking of large volumes of water (3–4 L daily)

2 The patients whose prepregnant hypertension seems to be lessened during pregnancy are of interest because a somewhat similar decrease of arterial pressure is regularly observed during pregnancy or pseudopregnancy in animals with experimental renal hy

untaught than *among* patients in more favorable economic and social circumstances This fact has no obvious explanation.

The structural lesions associated with but not necessarily characteristic of severe toxemia of pregnancy are renal hepatic cerebral pulmonary placental and possibly cardiac. The renal lesion is one of the most constant It consists *in thickening* of the glomerular basement membrane and proliferation of the glomerular endothelium The hepatic lesion seems to begin *in blocking* of portal capillaries by fibrin thrombi which in turn lead to peri

TABLE 13

A. Factors which may produce or accentuate relative ischemia or hypoxia of the placenta	B Examples (also known predisposing causes of pre-eclampsia)
1 Increased hydrostatic pressure within the intervillous lake	
a) From increased hydrostatic tension within uterus	Hydramnios Twins, triplets
b) From increased intra abdominal pressure	Primiparity Obesity with short stature
2. Diffuse mechanical compression of uterine blood vessels	Labor
3 Vasomotor constriction of spiral *arterioles* through autonomic nervous system	Extreme emotional tension or shock
4 Systemic disease producing widespread effect on arteries of uterus	Pre-existing hypertension Nephritis (?) Diabetes mellitus
5 Direct hypoxia of trophoblast by severe maternal anemia	Anemia of hookworm disease Sickle-cell anemia

portal necrosis This lesion at least insofar as can be estimated from liver biopsies, is more characteristic of severe toxemia with eclampsia than of pre eclampsia It is of course common in autopsy series The cerebral lesion consists essentially in edema and sometimes in areas of softening Lung capillaries like those of the liver may show diffuse fibrin thrombi Deposits of fibrin within the maternal placental vessels form the nuclei for the placental infarcts which are characteristically severe in toxemic pregnancy

The functional pathology is by no means as well worked out The primary lesion is probably placental Indeed E. W Page ad

teinuria, when proteinuria is defined as the excretion of more than 0.2 Gm of protein per 24 hours without hematuria or pyuria. Repeated, systematic examination of the urine—if need be only of the morning urine by a qualitative test—is therefore the means of recognizing the onset of this condition.

Thus the onset of proteinuria and abnormal weight gain in the last trimester of pregnancy in a patient whose blood pressure had hitherto been normal strongly suggest the onset of toxemia. Usually an increase in diastolic pressure at this time and some degree of edema will confirm the presumption. Gestational edema may mimic toxemia because of the edema which extends to the face and hands. Severe toxemia with arterial hypertension and retinopathy may simulate the syndrome of malignant hypertension. The patient whose blood pressure was elevated before the fourth month of pregnancy may have shown proteinuria as the result of hypertension; the superimposition of toxemia in such a case is heralded by an increase in proteinuria and diastolic pressure, together with increased water retention. The diagnosis of toxemia thus depends on the demonstration of proteinuria, edema and hypertension precipitated or increased by pregnancy, usually during its last trimester.

Causes of toxemia.—The definitive cause is unknown. It is known that toxemia is associated with structural or functional injury to the chorion. For this reason it appears only as the placenta reaches maturity and grows old. It is not observed in animals whose placenta is not of human type. It is five times more common in the first than in succeeding pregnancies. It is also predisposed to by hypertension and diabetes mellitus. Since these diseases are known to accelerate vascular senescence, their association with toxemia may depend on trophoblastic injury due to obliteration of uterine vessels in the placenta. This is suggested by the association of toxemia with extensive placental infarction. The incidence of toxemia is increased in women who suffer from inadequacies of hygiene and of diet so that it is more common among the poor and

death of birth of small ill nourished babies in toxemia and indications from enzyme studies of disturbed and inadequate placental function, weigh heavily in favor of the thesis His suggestion as to the mechanism of toxemia is that such hypoxia or ischemia results in liberation of degenerating trophoblastic syncytium into the maternal blood, and that one product of degenerating syncytium thromboplastin would account both for placental infarct and for fibrin deposits in liver and lung The mechanism of the renal lesion is less obvious nor is it altogether clear that it is the renal lesion which accounts for the access of arterial hypertension arteriolar constriction and capillary damage in organs other than liver and lung

Other and notable changes occur Normal pregnancy is associated with progressive increases in plasma content of various enzymes notably histamine angiotonase beta glucuronidase and pitressinase The onset of toxemia alters and sometimes intensifies these levels, while it also leads to a decrease in histidinuria Particular emphasis has been placed on the hormonal changes in toxemia which consist in increased urinary gonadotropin and decreased pregnandiol and estrogen Similar changes precede normal delivery In toxemia, their early onset during the last trimester is more probably evidence of premature placental senescence and degeneration than an etiologic factor

In the kidneys the injury to glomerular capillaries causes proteinuria because these capillaries become nonfiltering shunts possibly also by the opening up of preglomerular arteriocapillary shunts and of the juxtamedullary glomeruli the rate of glomerular filtration is decreased, while renal blood flow and tubular excretory functions may remain unaltered (Fig 14)

Origin of Edema

One of the oldest and most satisfactory observations on the clinical chemistry of toxemia the frequency of increased blood uric

vances the view that toxemia is the result of placental dysfunction due to diffuse hypoxia or relative ischemia of the maternal segment of the placenta This view is based in part on a comparison of fac

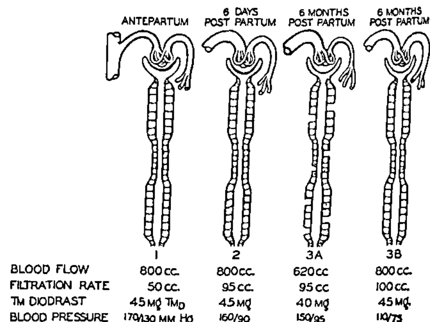


FIG 14—Schematization of renal changes in eclamptogenic toxemia of pregnancy *1* ante partum with afferent and efferent arteriolar constriction thickening of glomerular basement membrane preservation of normal renal blood flow and secretory capacity but depression of filtration rate and increase of blood pressure *2* a stage of recovery from (*1*) with residual constriction and hypertension *3A* essential hypertension as sequel to eclamptogenic toxemia depression of renal blood flow afferent arteriolar sclerosis and constriction efferent arteriolar constriction injury of tubular cells and secretory capacity *3B* recovery from eclamptogenic toxemia without residual functional or structural change Data are compiled from observations on two patients whose antepartum clinical status was very similar

tors which would have such effects on placental circulation with corresponding clinical factors known to predispose to pre-eclampsia (Table 13)

These clinical associations together with the frequency of fetal

death of birth of small ill nourished babies in toxemia and indications from enzyme studies of disturbed and inadequate placental function, weigh heavily in favor of the thesis His suggestion as to the mechanism of toxemia is that such hypoxia or ischemia results in liberation of degenerating trophoblastic syncytium into the maternal blood, and that one product of degenerating syncytium thromboplastin would account both for placental infarct and for fibrin deposits in liver and lung The mechanism of the renal lesion is less obvious nor is it altogether clear that it is the renal lesion which accounts for the access of arterial hypertension arteriolar constriction and capillary damage in organs other than liver and lung

Other and notable changes occur Normal pregnancy is associated with progressive increases in plasma content of various enzymes notably histamine angiotonase beta glucuronidase and pitressinase The onset of toxemia alters and sometimes intensifies these levels while it also leads to a decrease in histidinuria Particular emphasis has been placed on the hormonal changes in toxemia which consist in increased urinary gonadotropin and decreased pregnandiol and estrogen Similar changes precede normal delivery In toxemia, their early onset during the last trimester is more probably evidence of premature placental senescence and degeneration than an etiologic factor

In the kidneys the injury to glomerular capillaries causes proteinuria because these capillaries become nonfiltering shunts possibly also by the opening up of preglomerular arteriocapillary shunts and of the juxtamedullary glomeruli the rate of glomerular filtration is decreased while renal blood flow and tubular excretory functions may remain unaltered (Fig 14)

Origin of Edema

One of the oldest and most satisfactory observations on the clinical chemistry of toxemia the frequency of increased blood uric

acid and the relative infrequency of nitrogen retention, is not easily explained in terms of reduced glomerular filtration alone Both uric acid (in part) and urea are filtered from the plasma so that a reduction in glomerular filtration should have the same effects on the clearances of both, as, indeed seems to be the case (Bonsnes and Stander) Two factors may bear on the dissociation between uric acid and blood nonprotein nitrogen or urea nitrogen levels, (1) a possible increase in uric acid precursors as a result of syncytial degeneration and (2) the tendency to negative nitrogen balance common in toxemia, which in turn tends to depress the levels of blood urea Whatever the reason the facts stand that increased blood uric acid is common in toxemia and that the greater the increase the more ominous the prognosis And while blood urea is not often increased unless there is urinary suppression which indicates very severe disease the rate of glomerular filtration and consequently the rate of urea clearance, are usually depressed in rough proportion to the severity of the renal lesions It seems likely that the decreased glomerular filtration of water and salt, at a time when the tubules are already stimulated to salt reabsorption by the hormones of pregnancy enters into the clinical syndrome in that it leads to formation of urine of small volume relatively high specific gravity and low sodium and chloride content Thus by an abnormal mechanism another means of salt and water retention is added to the tendency to retention characteristic of normal pregnancy

Another mechanism of edema may be hypoproteinemia The increase of blood volume in pregnancy is due more to increase in water than to increase in solid content This hydremia is normally associated with a slight decrease of plasma protein concentration so that total protein content averages 6 5 Gm per 100 cc in normal pregnancy and plasma albumin 3 7 Gm Some further decrease of serum protein content is common in toxemia partly because of the renal lesion and also because it commonly arises on a background

of nutritional inadequacy Hypoproteinemia, particularly hypoalbuminemia, reduces serum colloid osmotic pressure and facilitates capillary filtration. Thus while the hypoproteinemia of toxemia rarely reaches the levels common in hypoproteinemic edema (5 Gm. total protein 2 5 Gm serum albumin per 100 cc.), it is sufficient to participate with the renal retention of salt and to increase the tendency to edema To the extent that hypoproteinemia is due to dietary lack it is important that it be relieved by administration of a diet containing a large amount of protein. Since saltless meat may be distasteful suitably flavored and diluted preparations of salt free milk powder (Ionalac*) may be added to the diet in doses of 10–20 Gm three to six times daily

In certain patients the hypoproteinemia cannot be explained by an inadequate diet or relieved by provision of protein or amino acids In these as in the nephrotic stage of glomerulonephritis it seems likely that the set of protein concentration is altered. This alteration may be in a sense homeostatic, for it facilitates the formation of glomerular filtrate and thus maintains urine formation through a thickened filtering surface When this seems likely it is unwise to transfuse vigorously with plasma and useless to feed large amounts of protein Indeed in severe cases in which convulsions have occurred or are imminent, the blood and plasma volume may be decreased and the plasma protein increased to about the normal in such cases anuria is common

Facial edema is probably associated with cerebral and retinal edema, which in turn causes headaches nervous irritability vomiting and scotomas

In toxemia the tendency to edema is often threefold There is salt retention of hormonal origin and retention as the result of decreased glomerular filtration To these are added hypoproteinemia The edema is clinically significant since it may be responsible for some of the symptoms and since it complicates the course and management, including delivery

Origin of Hypertension

The arterial hypertension is of unknown mechanism but is more probably of renal than of direct placental origin Possibly the renal pressor system (renin renin substrate, angiotonin) is set into action perhaps by increased intrarenal tissue pressure Renal ischemia, absent at the outset may appear as the process occludes large numbers of glomerular capillaries or as arteriolar vasoconstriction becomes intense The hypertension is thus similar in most respects to that of acute nephritis and the clinical syndrome, with its edema and tendency to convulsions, is reminiscent of acute nephritis in children Since the onset of the hypertensive state is sudden, the circulatory system does not have the opportunities for adjustment which are given by the slow onset of essential hypertension Thus the heart, while doubtless stimulated by the pressor agents, does not hypertrophy but it commonly dilates Functionally cardiac output tends to decrease as peripheral resistance is suddenly increased by extensive systemic arteriolar constriction As a result the pulse pressure does not widen as much as it does in established essential hypertension The arterial hypertension is therefore definitely diastolic Further Dexter and Weiss have shown that there may be imposed on the straining heart the added burden of extensive obliteration of pulmonary capillaries To the threat of pulmonary edema from failure of the left ventricle is therefore added the risk of right sided failure in cor pulmonale Perhaps the leading cause of death is cerebral hemorrhage This may have its origin in cerebral softening capillary and precapillary damage and in the accesses of arterial pressure during convulsions or hard labor

The arteriolar constriction of retinal vessels like that of acute nephritis and unlike that of established essential hypertension is more commonly segmental than evenly distributed in the vessel Sausage shaped constrictions are frequent and may be seen to shift slowly from one site to another When the process is intense the

spasm may all but obliterate the retinal arterioles. At this stage retinal edema is usually present, with papilledema and soft perimacular exudates Retinal detachment is a common sequel As hypertension persists acute arteriolar lesions similar to those of severe malignant hypertension may develop These may express a failure of the arterioles to adjust their walls to the strain of acute hypertension In other sites similar lesions probably account for some of the less common but very dangerous pulmonary placental retinal and renal manifestations notably transient hemoptysis abruptio placentae retinal hemorrhage cortical renal necrosis and hematuria

Toxemia Superimposed on Hypertensive Disease

Perhaps one third of patients with essential hypertension show some evidences of toxemia during pregnancy The incidence of toxemia as well as its severity may be greater in patients whose hypertension is of primary renal origin (glomerulonephritis pyelonephritis) although these constitute a very small proportion of patients with toxemia

The factors to be evaluated in determining whether or not hypertension in pregnancy is toxemic essential or a combination of both depend first of all on a knowledge of the patient s arterial pressure before and during the course of the pregnancy This history including the family history may be revealing When it is not the presence of cardiac enlargement with hypertrophy of pathologic left axis deviation and retinal arteriosclerosis with uniform constriction of the arterioles may lead to the diagnosis of essential hypertension The superimposition of toxemia on essential hypertension will be indicated by increased proteinuria, edema and other clinical symptoms

That a pre existing hypertension is renal rather than essential will be indicated by tests of renal function notably urea clearance in which a considerable deficit combined with an appropriate history and renal study may lead to the diagnosis of renal

Origin of Hypertension

The arterial hypertension is of unknown mechanism but is more probably of renal than of direct placental origin Possibly the renal pressor system (renin renin substrate, angiotonin) is set into action perhaps by increased intrarenal tissue pressure Renal ischemia, absent at the outset may appear as the process occludes large numbers of glomerular capillaries or as arteriolar vasoconstriction becomes intense The hypertension is thus similar in most respects to that of acute nephritis and the clinical syndrome with its edema and tendency to convulsions is reminiscent of acute nephritis in children Since the onset of the hypertensive state is sudden, the circulatory system does not have the opportunities for adjustment which are given by the slow onset of essential hypertension Thus the heart while doubtless stimulated by the pressor agents does not hypertrophy, but it commonly dilates Functionally cardiac output tends to decrease as peripheral resistance is suddenly increased by extensive systemic arteriolar constriction As a result the pulse pressure does not widen as much as it does in established essential hypertension The arterial hypertension is therefore definitely diastolic. Further Dexter and Weiss have shown that there may be imposed on the straining heart the added burden of extensive obliteration of pulmonary capillaries To the threat of pulmonary edema from failure of the left ventricle is therefore added the risk of right sided failure in cor pulmonale Perhaps the leading cause of death is cerebral hemorrhage This may have its origin in cerebral softening capillary and precapillary damage and in the accesses of arterial pressure during convulsions or hard labor

The arteriolar constriction of retinal vessels like that of acute nephritis and unlike that of established essential hypertension is more commonly segmental than evenly distributed in the vessel Sausage shaped constrictions are frequent and may be seen to shift slowly from one site to another When the process is intense the

to toxemia so as Strauss has shown the sodium retention of toxemia increases the severity of the vascular disease This treatment may be given without hospitalization it is usually accompanied by the recommendation of three or four hours of extra bed rest and the administration of a sedative such as phenobarbital (1½ gr) three or four times a day When a complete remission is thus obtained, pregnancy should be carried to term or until evidences of toxemia again appear

Since the syndrome may suddenly become intensified close observation is always desirable and is best achieved in the hospital Hospitalization is essential when the weight increases more than 2 lb weekly when proteinuria exceeds 5 Gm per 24 hours and when there is oliguria or hematuria, a systolic pressure greater than 170 mm. Hg encephalopathy vomiting epigastric pain or persistent visual disturbance

The characteristic encephalopathy of this disease is the eclamptic convulsion When this seems imminent, reassurance total quiet and sedation as with pentobarbital (3 gr 0 2 Gm.) are provided. *Convulsions may be prevented or treated by intravenous infusion* of a 2 per cent solution of magnesium sulfate given in a dose of 500 cc over a period of one hour The rate of infusion and the necessary dose are adjusted by repeated observations of the knee jerk a decrease is an indication for slowing or interrupting the infusion. An overdose causes respiratory failure long before the heart ceases to beat This accident is treated by prompt intravenous injection of a calcium salt (chloride gluconate or levulinate 1 Gm) and artificial respiration The infusion may be repeated at intervals of eight, 12 or 24 hours depending on response and the rate of urine formation In the presence of *oliguria early repetition* is inadvisable The injection of magnesium sulfate is followed by a feeling of warmth and torpor and central nervous system depression It should be noted that the dose of magnesium sulfate (1 or

hypertension (p 247) Severe renal hypertension like severe essential hypertension predisposes to an early onset and stormy course of superimposed toxemia

Thus, the presence of the two diseases in combination is a danger to the mothers in whom maternal mortality rises to about 15 per cent, and to the children in whom fetal mortality is 50 per cent and uncertain survival of damaged ill nourished babies adds still another toll It is especially this group of patients who exhibit some of the fatal mechanisms which appear in toxemia (cerebral hemorrhage, retroplacental hemorrhage pulmonary edema and anuria even the rare renal cortical necrosis)

Treatment of Eclamptogenic Toxemia

The syndrome is one of water retention arteriolar and capillary damage and acute hypertension Its palliative treatment is based on the relief of edema and symptomatic relief of complications notably convulsions Radical treatment depends on removal of the source—the trophoblastic tissue of the placenta

Palliation—The palliation of water retention depends on provision of a low sodium diet (less than 1 Gm sodium chloride daily) which is preferably low also in calories (about 1 500 daily) *but rich in protein (80–100 Gm daily) By this means,* further accumulation of salt and water is prevented and the body is depleted of some of its salt store When there is no oliguria, the rate of urinary depletion of sodium may be increased by a water intake up to about 3 L daily and administration of potassium or ammonium salts Since toxemia is usually associated with decreased alkali reserve, to which also the normal pregnant woman seems especially susceptible ammonium salts should be cautiously and intermittently given The recession of edema is often followed by amelioration of the vascular disturbance Indeed just as excessive water and salt retention in pregnancy seem to some to predispose

vascular degeneration in the placenta, their use might contribute to prevention of toxemia. (2) Also aimed at prevention is administration of diethylstilbestrol (dose is 0 5 mg × the week of pregnancy at the time of treatment, until two weeks before term) This method, aimed at correction of hormonal imbalances is suggested for use in women suffering from diabetes mellitus or hypertension i.e., from conditions predisposing to toxemia The concept on which it is based is not generally accepted and its application is still experimental (3) The revived use of Veratrum viride in the control of hypertension and encephalopathy of severe toxemia is gaining adherents It probably should be considered an adjunct to the modes of treatment previously outlined and one only to be used under carefully controlled conditions

Two forms of treatment have still only experimental interest. One based on the view that release of thromboplastin in degenerating trophoblast underlies the lesion of toxemia consists in heparinization. The other based by the Smiths on the view that the toxic material released from the placenta is akin to menstrual toxin consists in injection of a pseudoglobulin antagonist. What appear to be favorable results followed application of both procedures to small groups of patients In severe complications of toxemia notably pulmonary edema and anuria alone or in combination Hingson and also Dieckmann reported dramatic responses from continuous high caudal or spinal anesthesia.

Radical treatment—In every severe case and in those mild cases which arise long before term the advisability of terminating pregnancy preferably by nonoperative means must be considered. The signs which may demand it are listed in Table 14 and the indications summarized in the following paragraphs Operation during eclampsia is contraindicated since it doubles mortality The aim here is to revert the status to one of controlled pre-eclampsia before intervening

2 Gm intramuscularly every four or six hours) customarily given in the treatment of eclampsia is not sufficient to cause a response which persists for much more than an hour Alternatively, the convulsion may be treated by slow intravenous injection of a barbiturate such as sodium amytal® (7½ gr, 0 5 Gm) It is probable that an adequate dose of magnesium sulfate which causes vasodilatation as well as cerebral and neuromuscular depression is more beneficial and less dangerous than sedation alone Combined treatment with magnesium sulfate and veratrum is gaining support

The convulsions may be followed by a prolonged stupor or by pulmonary edema right heart failure or a state of shock with hemoconcentration and anuria These complications sometimes occur without convulsions The stuporous state may be treated as is oliguria or anuria by the infusion of glucose 500–1 000 cc of 20 per cent solution, given over one hour and repeated every six to eight hours Anuria may be considered relieved when the urine volume reaches 30 cc per hour The complications of pulmonary edema and right heart failure are treated by prompt venesection (300–500 cc of blood) or bloodless phlebotomy (p 218) and administration of 100 per cent concentration of oxygen and rapid digitalization by intravenous injection of digitoxin (p 216) The state of shock is treated by the infusion of plasma or of concentrated albumin at a rate regulated by clinical response and frequent examination of the respiratory and cardiac action During the infusion the venous pressure should not be permitted to become greatly elevated the lungs should show no increase in rales and the heart should not speed its rate

Three modes of treatment whose value is still conjectural deserve mention (1) Administration of thyroid extract during pregnancy to prevent toxemia in women whose body build or other indications suggest that toxemia may supervene has not yet been firmly established If as in theory they might thyroid and iodine will retard

vascular degeneration in the placenta their use might contribute to prevention of toxemia. (2) Also aimed at prevention is administration of diethylstilbestrol (dose is 0 5 mg × the week of pregnancy at the time of treatment until two weeks before term) This method aimed at correction of hormonal imbalances is suggested for use in women suffering from diabetes mellitus or hypertension i e., from conditions predisposing to toxemia The concept on which it is based is not generally accepted and its application is still experimental (3) The revived use of Veratrum viride in the control of hypertension and encephalopathy of severe toxemia is gaining adherents It probably should be considered an adjunct to the modes of treatment previously outlined and one only to be used under carefully controlled conditions

Two forms of treatment have still only *experimental interest.* One based on the view that release of thromboplastin in degenerating trophoblast underlies the lesion of toxemia consists in heparinization. The other based by the Smiths on the view that the toxic material released from the placenta is akin to menstrual toxin consists in injection of a pseudoglobulin antagonist. What appear to be favorable results followed application of both procedures to small groups of patients In severe complications of toxemia notably pulmonary edema and anuria alone or in combination Hingson and also Dieckmann reported dramatic responses from continuous high caudal or spinal anesthesia.

Radical treatment—In every severe case and in those mild cases which arise long before term the advisability of terminating pregnancy preferably by nonoperative means must be considered. The signs which may demand it are listed in Table 14 and the indications summarized in the following paragraphs Operation during eclampsia is contraindicated since it doubles mortality The aim here is to revert the status to one of controlled pre eclampsia before intervening

TABLE 14—INDICATIONS FOR TERMINATION OF PREGNANCY (DIECKMANN)

A Systolic blood pressure is constantly 170 mm Hg or shows a persistent daily increase

A Proteinuria always exceeds 5 Gm per 24 hours, or the qualitative test of the 24 hour urine is 3 plus

A Weight gain exceeds 100 Gm per day

A Marked edema suddenly occurs

B Cerebral visual or gastrointestinal symptoms arise

B Oliguria, anuria or hematuria occurs

B Jaundice develops

B Blood nonprotein nitrogen is 50 mg per cent or more

B Pulse rate is 120 or more

B Edema of the lungs or cyanosis is present

B Blood shows an increasing concentration as indicated by an abnormally high or increasing hemoglobin content cell volume, serum protein concentration or specific gravity

The advisability of terminating the pregnancy is dependent on the duration of the gestation the severity of the symptoms and signs, and the condition of the cervix.

'*Gestation of twenty six weeks or less* should be terminated if more than one of the above listed criteria (Table 14) are present or if there is no appreciable improvement after seven days of adequate treatment

Gestation of twenty seven to thirty one weeks should be treated medically until thirty two weeks unless some B signs develop or the A signs persist despite treatment or increase in degree

Gestation of thirty two to forty weeks if B signs are absent, should be treated medically until the cervix is ripe when induction of labor will be successful If the A signs increase in degree or if any of the B signs appear the pregnancy should be terminated either by (1) rupture of the membranes and/or insertion of a bag or (2) cesarean section if the cervix is uneffaced and closed

'*Our results indicate that the careful medical management of the toxemic patient if begun early enough will usually prevent further increase in the severity of the symptoms and signs until the cervix is ripe*' This means that labor can usually be successfully induced by rupture of the membranes

The patient who does not respond to *treatment*, or has been neglected, is treated by rupture of the membranes and/or the insertion of a bag if the cervical canal is less than 2 cm. long, or if there is no effacement and dilatation, by cesarean section under local anesthesia."

NOTE.— A signs are those ordinarily present in pre-eclampsia B signs characterize the intensification or complication of the disease process.

To Dieckmann's indications for the termination of pregnancy we believe should be added the persistence under medical management of the signs of toxemia moderately severe or severe for three or more weeks Cases of mild toxemia (blood pressure 150/90 or less trace to 1+ proteinuria scant or receding edema) may be carried longer in the interests of a viable child without as far as has been shown injuring the mother The recommendation for interruption in prolonged resistant toxemia of more than average severity is based on the fact, first shown by Herrick and Tillman and since widely confirmed that in 20–30 per cent of toxemic women normotensive before and during the early months of pregnancy essential hypertension develops either soon after *delivery* or after the lapse of months However evidence of Chesley Somers and Vann indicates that the incidence of post toxemic hypertension can be reduced to 8 per cent or less by treatment along lines suggested here Some observers believe that this association is evidence of the genetic similarity of toxemia and hypertension and that pregnancy in such patients has merely made manifest a latent hypertensive trait That this is probably not the case is indicated by the comparatively low incidence of hypertensive disease in women who have had adequate treatment of toxemia.

Consequently the presumption is that the renal vascular lesions of toxemia may lead to postpartum hypertension *in patients in* whom it might not otherwise have developed. From this point of view the occurrence of post toxemic hypertension can be related to the duration of the process and the consequent irreversibility of the lesion rather than to the severity of toxemia. Thus the preven

tion of hypertension seems to depend on interruption of pregnancy when toxemia is prolonged or when it does not fully remit under medical management

The Fetus

The consideration of hypertension and toxemia and their admixture has thus far proceeded without reference to the fate of the fetus It seems unlikely that the fetus is directly injured by the pressor agents of hypertension or a toxin of toxemia Rather, the prognosis depends on its nutrition and this on the integrity of the placental circulation The maternal placental vessels pass through a life cycle from youth to senility during nine months Thus, in comparison with vessels elsewhere they are excessively plastic in the changes they undergo with the passage of time While less plastic arterioles elsewhere in the body can maintain themselves in the face of hypertension through many years of slow degeneration, placental vessels seem to be abnormally sensitive to its effects Possibly for this reason they tend to mature and obliterate at an abnormally rapid pace in patients with essential hypertension It is probably in this manner that hypertension predisposes to toxemia and that toxemia intensifies placental injury and that alone or combined they cause increased fetal loss The fetal injury is reflected in a sum of abortions premature births stillbirths and neonatal deaths which average 35 per cent and reach more than 50 per cent in severe essential hypertension and about 7 per cent in mild cases Thus the prognosis for the fetus of the hypertensive patient is much more serious than that for the would be parent who unless severe toxemia is superimposed and allowed to run its course emerges unscathed

Prognosis

The combined risks to mother and fetus of hypertension and toxemia demand that the desirability advantages and risks of preg

nancy be carefully evaluated in the hypertensive patient.

The purpose of pregnancy is the birth of a healthy child who may be brought up to maturity by the parent. The primary end birth itself may be frustrated by the presence of hypertension further the mother may not be physically able to participate in the child's upbringing The effects of such failure in pregnancy and up-bringing should be carefully considered in advising pregnancy

Three types of patients require prognostic consideration before or early in pregnancy These are (1) those who have had toxemia but show no residue of cardiovascular disease (2) those who have prepregnant essential hypertension and (3) those with post toxemic hypertension The guiding considerations for prognosis are (1) that toxemia occurs in 6–9 per cent of all pregnancies and (2) that fetal mortality averages about 10 per cent and maternal mortality 1 per cent in toxemia

The problem of the normotensive post toxemic patient is answered by the fact that a former toxemia approximately doubles the probability of toxemia in a subsequent pregnancy bringing the incidence to 20 per cent. Further the recurrence of toxemia increases the probability of persistent postpartum hypertension Therefore pregnancies subsequent to one complicated by toxemia carry an increased risk of which the patient should be made aware The risk is not great It is probably greater in families whose history suggests a predisposition to hypertension. It is sufficient risk to require antepartum care under better than average conditions

The patient with prepregnant essential hypertension has as we have noted a 50–70 per cent chance of passing through pregnancy unharmed The probability is greater when the hypertension is mild and previous pregnancies have not been complicated by toxemia The incidence of toxemia mild or severe in the average hypertensive woman is about 30 per cent. The probability of fetal loss varies from 7 to 50 per cent, depending on the severity of the arterial disease and the level of blood pressure Further if by premature de

livery, deliberate or not a living child is obtained, the child is often small, and it should be remembered that those who weigh less than 2 kg have less than an even chance of survival The patient with mild hypertension who is young, has passed through pregnancy without toxemia and whose vessels and heart are well adjusted to the presence of hypertension has little more than a normal personal risk in pregnancy, although more than the normal chance of disappointment in its result In patients with moderate or severe hypertension and evidences of sclerosis the condition will be aggravated by pregnancy and in 10 per cent life will be jeopardized Such patients have less than an even chance of giving birth to a healthy or even a viable child It is unlikely that they will be physically able to care for the offspring through childhood Thus, with mild hypertension pregnancy need not be discouraged with severe hypertension it is contraindicated

In a few patients a favorable response to sympathectomy has been shown to permit them to go through normal pregnancies But in severe essential hypertension the game is not worth the candle Especially when symptoms of toxemia appear early in pregnancy, the presumption is that the fetus is lost in any case and therapeutic abortion is indicated

BIBLIOGRAPHY

American Committee on Maternal Welfare Classification of the toxemias of pregnancy The Mother 1 13 17 April 1940

Bonsnes R W and Stander H J Survey of 24 hour uric acid and urea clearances in eclampsia and severe pre eclampsia J Clin Investigation 25 378 1946

Browne F J Chronic hypertension and pregnancy Brit M J 2 283 1947

Burwell C S The placenta as a modified arteriovenous fistula Am J M Sc 195 1 1938

Chesley L C and Annitto J E A study of salt restriction and of fluid intake in prophylaxis against pre-eclampsia in patients with water retention Am J Obst & Gynec 45 961 1943

——— Pregnancy in patient with hypertensive disease Am J Obst & Gynec 53 372 1947

Corcoran A C and Page I H Renal function in late toxemia of pregnancy Am J M Sc 201 385 1941

Dexter L and Weiss S Preeclamptic and Eclamptic Toxemia of Pregnancy (Boston Little Brown and Company 1941)

DIECKMANN W J The Toxemias of Pregnancy (St. Louis C. V Mosby Company 1941)
EASTMAN N J AND WHITRIDGE, J., JR. The prevention of toxemia of pregnancy J A. M. A. 120 729 1942.
IRVING, F C. Treatment of eclampsia and pre eclampsia with veratrum viride and magnesium sulfate Am. J Obst. & Gynec. 54 731 1947
NEWELL, J L., AND SMITHWICK, R. H Pregnancy following lumbodorsal splanchnicectomy for essential and malignant hypertension, New England M J 236 851 194
PAGE, E. W Placental dysfunction in eclamptogenic toxemias, Obst. & Gynec Surv 3 615 1948
—— in Conn H. F (ed) 1949 Current Therapy (Philadelphia W B Saunders Company 1949)
—— AND OGDEN E. The physiology of hypertension in eclampsia Am. J Obst. & Gynec. 38 230 1939
—— PATTON H. S AND OGDEN E. The effect of pregnancy on experimental hypertension, Am. J Obst & Gynec. 41 53 1941
RODBARD S AND KATZ, L. N The effect of pregnancy on blood pressure in normotensive and hypertensive dogs Am. J Obst. & Gynec. 47 753 1944
SMITH, O W SMITH G V AND HURWITZ, D Increased excretion of pregnandiol in pregnancy from diethylstilbestrol with special reference to prevention of late pregnancy accidents, Am J Obst. & Gynec. 51 411 1946.
STRAUSS M. B Observations on the etiology of the toxemias of pregnancy I. The relationship of nutritional deficiency hypoproteinemia and elevated venous pressure to water retention in pregnancy Am J M. Sc 190 811 1935
—— II Production of acute exacerbation of toxemia by sodium salts in pregnant women with hypoproteinemia, ibid 194 772 1937
WELSH, C A WELLEN I AND TAYLOR, H C. JR. Renal blood flow filtration rate and tubular excretory mass in patients with specific toxemia of pregnancy J Clin. Investigation 20 438 1941
WINKLER, A. W SMITH P K. AND HOFF H E Intravenous magnesium sulfate in the treatment of nephritic convulsions in adults, J Clin. Investigation 21 07 1942

SECTION V

14 Special Forms of Medical Treatment

No ONE WHO has watched the course of medical treatment in hypertension over years can fail to be impressed by the divergencies of claims and results as remedy after remedy has its brief course on the stage As a result some workers have become therapeutic nihilists while others have remained enthusiasts who join each new battalion of the credulous and hopeful There is of course, a mean

Analysis shows that the uncertainties of the field are due to a variety of factors The first and greatest is that the etiology and mechanism of essential hypertension remain unknown Opposed to this are the right the patient feels he has to have something done for him and the duty the physician feels to fulfil this demand One important variable is the patient s state of mind the effect on it of the simple patient physician relationship with or without a pink pill and the effect of external circumstances As Ayman has pointed out symptoms in most cases of early hypertension are not due to hypertension but like the hypertension are evidences of disturbed psychic and vasomotor function Their temporary relief by simple and nonspecific means is therefore almost assured This fact with factors not yet measurable make the course of the dis ease sometimes even when it is well established unpredictable to a

degree But until more information comes from research little can be done to change this situation

What can be corrected is the tendency of some physicians to view all hypertension as a single and insoluble problem so that they neglect the safeguards and advantages of careful diagnosis and evaluation. Another a related error is the trust in some simple magical cure sufficient in itself which will dispense with the need for effort in doing the things that are at hand to be done and that are effective

For all these reasons treatment in hypertension is controversial As each new remedy appears tempers rise and recede as it is put in its proper niche if indeed it has one From each of these episodes the careful observer learns a good deal because each focuses attention on some particular aspect of the mosaic of hypertensive disease In all this *Sturm und Drang* it is occasionally wise to say very quietly And forgive us our trespasses even as we forgive those who trespass against us

I THIOCYANATE

Evaluation of thiocyanate like most drugs used in hypertension has required years and is not yet fully agreed on Unlike many drugs which have been used and dropped thiocyanate has recently returned to favor which now seems again to be ebbing It was first recommended as a hypotensive agent in hypertension by Pauli in 1903 Some enthusiasts more or less uncritically praised its effects but its use was desultory in 1928 the feeling and evidence in its favor were inadequate to resist the report of two deaths attributed to its administration

Nor is there adequate knowledge of its pharmacologic action. Thiocyanate is thought by some to have a slight depressant action on the central nervous system This accords with our experience but needs quantitative verification Its classic toxic action on smooth muscle is one of relaxation so it is claimed to act as an arteriolar

vasodilator, but that it acts in this way in nontoxic concentrations is not established Also it is believed to act in hypertension by reducing the basal metabolic rate, this indeed is one of its toxic side effects but is not established as a basis of its therapeutic effect. Recently it has been shown to depress cardiac output, and this may account for part of its hypotensive effect

No penetrating consideration was given its use until 1936 when the late M H Barker showed that the serum thiocyanate level could be used to determine the level of desirable dosage and to offset the danger of overdosage Since then it has been more widely used than ever before Most competent observers believe that it has value, although others oppose its use as dangerous or believe it has no more value than any placebo To this day many physicians use thiocyanate without proper regard for the safeguards of observation and repeated measurement of blood thiocyanate which must surround its administration The reckless use of thiocyanate is one factor that is again bringing it into disrepute

Administration —Barker suggested that the drug be given in small slow increments feeling the way until a maximal therapeutic response is observed Experience has taught that the therapeutic level for most patients lies between 6 and 12 mg of thiocyanate per 100 cc of serum The level is lower in some patients in whom a level of 4 mg per 100 cc may be quite as effective and much more tolerable than a higher concentration Symptoms and signs of toxicity usually appear when the level passes 15 mg per 100 cc and whereas they may not appear at this level it is certainly undesirable to exceed it

There are many ways of starting administration of the drug One is to give 0 2–0 3 Gm (3–5 gr) in two daily doses and after a week to find the serum thiocyanate concentration and adjust the dosage as indicated In this method as in any other each patient offers an individual problem whose clinical response is carefully evaluated during frequent determinations of serum thiocyanate

level. These determinations are repeated weekly until a satisfactory level is secured, then repea ed at two weeks at four weeks and at least, at six week intervals thereafter The usual maintenance dose varies from three to 21 doses of 0 3 Gm (5 gr) each week. The plasma level once apparently set in a patient, may change without explanation. Thus there is no set level of dosage. The form in which the drug is given is unimportant either the sodium or the more customary potassium salt may be used. The salt may be given in flavored aqueous solution or in tablets enteric-coated or not. Whatever the form used it had best be adhered to A change from aqueous solution to enteric-coated tablets may demand a consider able increase of dosage for some of these may pass through the gastrointestinal tract undissolved.

The chemical determination of serum thiocyanate is easily within the range of competence of any hospital clinical laboratory and of many office laboratories Methods which unnecessarily sac rifice accuracy for simplicity should not be used

In summary (1) there is no set dosage of thiocyanate either from patient to patient or in the same patient under different con ditions for its excretion is widely variable (2) therefore the use of thiocyanate should not be attempted unless the physician can measure the concentration of the drug in the blood at suitable in tervals and with reasonable (5–10 per cent) accuracy

Selection of patient —Some clinicians believe that a trial with thiocyanate is justifiable in all patients who do not exhibit specific contraindications Others would limit its use to the early stages of the disease whether or not there are annoying symptoms We and oth rs use it only for symptomatic relief and when other measures have not been fully effective

The contraindications to its use are more generally agreed on. Patients over age 60 and patients of any age with severe cerebral or generalized arteriosclerosis do not respond well but usually become dull and confused. Some of them become depressed and

hallucinated Severe depression of cardiac and/or renal function are also contraindications Neither the malignant syndrome nor hyper tension of toxemic pregnancy is benefited by its use Angina pec toris is usually considered another contraindication, since thiocyanate sometimes increases the frequency of anginal attacks Still, in occa sional patients the cardiac pain seems to be lessened by thiocyanate Most, if not all, such patients are those whose pain is precordial vague irregularly recurrent and not true angina pectoris Their re lief from thiocyanate may reflect a sedative effect in cardiac neu rosis

With these contraindications and the possibilities of intoxica tion in mind, it is apparent that thiocyanate should not be used indiscriminately Further many patients with minimal symptoms and moderate levels of arterial hypertension carry on more satis factorily under carefully applied general measures of treatment than they do with a drug on which they tend too much to rely

There remain two large groups in which thiocyanate seems to be of definite benefit The first includes patients with severe head ache who are so harassed by pain that a vicious circle of anxiety and tension is created For these thiocyanate is often a sovereign remedy A subgroup is made up of those who complain of tinnitus or dizziness these also may be greatly benefited The second group includes patients whose diastolic pressure is high (roughly 115 mm Hg or more) and who do not show advanced retinal arteriosclero sis In such patients repeated examinations at intervals of six months may begin to show the onset of failure of vascular adaptation manifested in increasing cardiac size or symptoms loss of renal con centrating ability increasing retinal arteriolar sclerosis or a tend ency to increase in diastolic and systolic pressures The administra tion of thiocyanate to such patients may lead to deceleration of the apparent progress of the disease Thiocyanate may also be used for migraine not due to hypertension Since it also seems to have a sedative effect its greatest value may be in forms of the disease in

which psychogenic and neurogenic factors are of major importance

Results—One of the most dramatic and satisfying effects is the relief of headache and this alone may justify its use Reduction of blood pressure and the relief of exertional dyspnea are much less common.

The long term results are not easily evaluated In theory reduction of arterial pressure might prolong life by slowing the development of arteriolar sclerosis Originally the drug was intended to prevent sclerosis by acting directly on the vessels. This effect is not confirmed although there is evidence that thiocyanate retards lipid deposition in experimental cholesterol atheroscletosis Roughly a third of suitably selected patients show a fall of pressure of from 20 to 40 mm. Hg systolic and from 10 to 15 mm diastolic during the first weeks of treatment at therapeutic serum concentrations If the pressure does not fall and if no other clinical benefit is observed after a trial of six to eight weeks with blood concentration up to 12 mg per 100 cc thiocyanate should be discontinued Its use may again be attempted when the disease enters some other phase or when an indication for its use such as headache appears Barker and Davis made the interesting observation that patients who do not respond to the drug before sympathectomy may respond after the operation Others suggest that it adds to the efficacy of low sodium diets

A typical example of the use of thiocyanate in 100 patients whose hypertension ranged from mild to very severe may aid the reader in evaluating the drug Nearly all had been observed for some months and treated by other means Some symptomatic relief principally of headache was noted in 66 subjects and in 31 of these it was almost complete Only one quarter of the patients showed sustained lowering of arterial pressure (*mean* 26 mm Hg systolic and 19 mm diastolic) A significant number commented on the relief of insomnia and on release of emotional tension and instability Within 48 hours of *administration* early signs of toxicity

may develop Thus, 24 patients complained of asthenia Nausea vomiting and diarrhea were less common But reassurance, symptomatic treatment and further slow increase in thiocyanate dosage permitted its continued use in 12 of these patients The other 12 remained intolerant These toxic signs were never cause for serious concern

At intervals which varied from two to 54 months after beginning treatment 15 patients developed delayed toxic manifestations. Eleven complained of dermatitis or purpura and two showed signs of hypothyroidism with myxedema and thyroid enlargement

Symptoms and signs of toxicity—The less serious signs and symptoms of toxicity which may appear at commonly tolerated blood levels are those which appear at the outset of treatment During the first few weeks, patients often notice weakness and fatigability and sometimes decreased libido Indeed, these are so common that they can hardly be considered manifestations of toxicity They often pass off after a few weeks despite continued administration of the drug The lassitude may help the patient to reduce the pace of his daily life Occasionally nausea, vomiting and diarrhea are so severe that the drug must be discontinued The delayed evidences of toxicity are more serious Some are probably due to sensitization

Erythematous dermatitis, with or without pruritus is seen from time to time This clears up rapidly on withdrawal of the drug and does not necessarily reappear when it is given again Maculopapular eruptions are also common They too disappear on drug withdrawal Occasionally solitary papules appear on mucous surfaces Severe purpura is less common than dermatitis although usually present in mild degree in the other eruptions

Overdosage so that the serum content rises to toxic levels induces nausea vomiting and severe anorexia These are harbingers of impending intoxication As the blood levels of thiocyanate rise serious complications appear Especially in older persons slurring of speech may be the first symptom often followed by the appear

ance of an unsteady gait. Disorientation and hallucinations may occur It is important to differentiate this condition from hypertensive encephalopathy The end stage is coma sometimes with a hemorrhagic diathesis which affects the central nervous system diffusely Exfoliative dermatitis is by far the most serious cutaneous manifestation of toxicity Alopecia is not common Bizarre painful forms of peripheral neuritis are occasionally caused by thiocyanate Osteoporosis with local joint pains and swelling similar to those of traumatic osteoporosis has been reported in 2 per cent of patients given thiocyanate over long periods It is suggested that those taking the drug be encouraged to maintain a high calcium intake

There have been isolated reports of cerebral thrombosis thought to be related either to thiocyanate toxicity or to the fall in blood pressure elicited Neither seems a very good explanation for a phenomenon so common among hypertensives

Since thiocyanate causes goiter when fed to animals it is not surprising that it should do so in patients Several instances have been reported and two were observed in our series of 100 patients The goiter is associated with hypothyroidism and sometimes with clinical myxedema In this condition blood iodine values are low and there is increased urinary excretion of thyrotrophic hormone in the inactivated form. Thiocyanate goiter is relieved by administration of thyroid substance (0 1 and 0 2 Gm 1½ and 3 gr) on alternate days even though thiocyanate is continued for the treatment of hypertension Thyroid substance bypasses the block to the formation of thyroid hormone by the thyroid. Since iodine deficiency predisposes to thiocyanate goiter small doses of iodide may be given during treatment with thiocyanate

We reiterate that signs of severe toxicity are rare if proper care is taken to keep the thiocyanate blood content below the toxic level Occasional patients probably have an idiosyncrasy to the drug just as with almost all therapeutic substances but its importance need not be exaggerated Since the body content of the drug is dis

may develop Thus, 24 patients complained of asthenia Nausea vomiting and diarrhea were less common But reassurance, symptomatic treatment and further slow increase in thiocyanate dosage permitted its continued use in 12 of these patients The other 12 remained intolerant These toxic signs were never cause for serious concern

At intervals which varied from two to 54 months after beginning treatment, 15 patients developed delayed toxic manifestations. Eleven complained of dermatitis or purpura, and two showed signs of hypothyroidism with myxedema and thyroid enlargement

Symptoms and signs of toxicity —The less serious signs and symptoms of toxicity which may appear at commonly tolerated blood levels are those which appear at the outset of treatment. During the first few weeks, patients often notice weakness and fatigability and sometimes decreased libido Indeed these are so common that they can hardly be considered manifestations of toxicity They often pass off after a few weeks despite continued administration of the drug The lassitude may help the patient to reduce the pace of his daily life Occasionally nausea vomiting and diarrhea are so severe that the drug must be discontinued The delayed evidences of toxicity are more serious Some are probably due to sensitization

Erythematous dermatitis with or without pruritus is seen from time to time This clears up rapidly on withdrawal of the drug and does not necessarily reappear when it is given again Maculopapular eruptions are also common They too disappear on drug withdrawal Occasionally solitary papules appear on mucous surfaces Severe purpura is less common than dermatitis although usually present in mild degree in the other eruptions

Overdosage so that the serum content rises to toxic levels, induces nausea, vomiting and severe anorexia These are harbingers of impending intoxication As the blood levels of thiocyanate rise serious complications appear Especially in older persons slurring of speech may be the first symptom often followed by the appear

blood vessels as observed in the eyegrounds Renal function in most cases has shown at least temporary improvement. Looking back on the experience of several years mostly in the treatment of rapidly advancing or very advanced malignant hypertension it is apparent (1) that a few patients have shown lasting remissions (2) that nearly all but those in renal failure showed temporary remissions and (3) that the duration and adequacy of remission vary roughly with the level of renal function as measured by secretory capacity The clinical experiments are therefore being continued.

There is still great uncertainty regarding the best method of preparing the extracts. The search is long and slow as there is no biochemical method of assaying extracts and no chemical knowledge of the active principle to guide in their separation While these limitations prevail the use of kidney extracts is only experimental

The occurrence of reactions to their injection complicates the results A curious thing about these reactions is their unpredictability Weeks or months may go by without one then suddenly one occurs There may be a series of them followed by a period of complete freedom

The reactions are usually characterized by a profound fall in arterial pressure which may persist for minutes to hours and be associated with pains in the muscles of the back and chest. Alarming as they are no serious sequelae have been observed of the many we have seen We are still unable to decide how much influence they have on the therapeutic effects of the extract. Reactions of this sort do not occur in dogs or rats hence, studies in these animals do not aid in the analysis of the problem Despite this lack of reactions blood pressure may be reduced in them from hypertensive to normal levels

There is also some relation between local reactions to the extract and the fall in blood pressure, but again it is not direct and invariable Severe local reactions may occur with or without fall in arterial pressure

solved in the extracellular fluid, dehydration, as from vomiting severe diuresis or impending uremia, will cause the concentration to rise, sometimes to toxic levels A review of the evidence fails to reveal any death or serious injury in patients who were under adequate supervision and whose blood levels were controlled at appropriate intervals

Treatment of intoxication—On the first sign of severe intoxication, the drug should be discontinued Excretion may be hastened by administration of large amounts of water by mouth and hypertonic salt by vein The reasons for intoxication should be investigated Renal failure or severe sensitivity contraindicate readministration

II KIDNEY EXTRACT

From knowledge of the physiology and biochemistry of the kidneys there are reasons for believing that they contain a substance or substances which inhibit the action of certain pressor substances (p 256) Attempts have been made to separate such an inhibitor which might have therapeutic value Put briefly, the following results have been obtained

Protein containing extracts of hog beef and sheep kidneys have been prepared which lower arterial pressure in experimentally hypertensive rats and dogs Especially in dogs with renal hypertension in the malignant phase the therapeutic action of these extracts is demonstrated by the disappearance of hemorrhage both ocular and gastrointestinal This much now is established and the results have been confirmed by a number of investigators

In patients the results have been erratic and complicated by foreign protein reactions which tend to obscure any possible specific effects of the extracts Some types of extracts lower blood pressure and associated therewith hemorrhages and papilledema may disappear if they were initially present Indeed one of the most striking effects of various extracts is their seeming action on the

eral renal function was improved, although some patients showed a decrease in glomerular filtration rate particularly noticeable was improvement in concentrating power Remissions persisted for an average of 24 months and extend to 30 months

The other 19 patients responded similarly but the responses were quantitatively weaker and poorly sustained so that most of them have died, some of them during treatment. The most definite

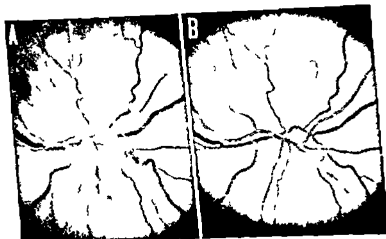


FIG. 15—Eyegrounds of patient with malignant hypertension *A* before and *B* three months after treatment with pyrogen. Improvement is obvious.

difference between the groups was the level of Tm_{PAH} This function averaged 62 mg per minute per 1 73 sq m (range 48–109) in the 16 who responded well and only 26 mg (range 12–40) in those showing poor responses In contrast, arterial pressure retinopathy and the degree of cardiac disability gave no clue to the outcome of treatment. It would seem that the capacity to respond well to pyrogen is determined by the extent to which arteriolar sclerosis has advanced in the kidneys We do not believe that this relationship is evidence of a specific correlation between renal excretory

Clearly, it would be premature to attempt to form any considered judgment about these extracts They are neither to be touted as established therapeutic agents nor to be condemned as failures. Empirically their use to control malignant hypertension may be justified, scientifically the effort to elucidate the mechanism of their activity should be continued

III PYROGEN

In normal subjects the delayed response to pyrogens after the chill is a widespread vasodilation especially evident in the renal vascular bed Thus, we and others have demonstrated consistent increases in renal blood flow even to 100 per cent, in the 24 or 36 hours after a pyrogenic reaction to the most varied materials and thus in normal and hypertensive human beings and dogs While, in hypertension reduction of blood pressure is most obvious during the early hours of the vasodilation (e g four hours after the chill) some decrease commonly persists for 24 or 48 hours The frequency of such reactions in patients given kidney extract led us with Taylor to study the effects on malignant hypertension of pyrogenic agents which could hardly of themselves be specifically related to hypertensive pressor mechanisms

A summary of observations was presented at the 1948 meeting of the Central Society for Clinical Research Briefly 25 patients with malignant hypertension were treated, most of them with a water soluble pyrogen of bacterial origin (pyromen* Baxter Laboratories Inc) In 16 patients in whom the response was good, the average control diastolic pressure of 126 mm Hg was reduced to 100 mm Hg in five to 19 weeks Papilledema receded in all but two Retinal hemorrhages regressed in 14, as did the fresh retinal exudates In five congestive heart failure unresponsive to ordinary management was relieved Improvements in electrocardiograms and decreases in heart size (average control + 18 per cent enlargement average during treatment + 5) were noted In gen

IV RUTIN

In 1936 Szent Gyorgyi proposed the name vitamin P for a substance or group of substances present in paprika and lemon peel believed to restore increased capillary permeability to normal This was the beginning of interest in substances of the general nature of flavone glucosides now widely used clinically in all manner of diseases

The true value of vitamin P like flavones has never been accurately determined principally because increased capillary permeability has no cleancut clinical equivalent. The terms capillary permeability resistance and fragility have been neither accurately defined nor measured although they are used confidently by many clinicians For this reason much that has been written and this applies chiefly to the unrestrained literature of the drug houses can be accepted only with large reservations

It is still uncertain precisely what substances were responsible for the vitamin P activity of lemon peel or citrin but most evidence suggests it to be hesperidin chalcone Both the clinical and laboratory reports on vitamin P have been unsatisfying and contradictory so that after 12 years little can be said with confidence as to its clinical application

The structural similarity of hesperidin and rutin led Couch to suggest that the latter might be a better source of vitamin P activity than paprika or lemon rind. Rutin is a flavone glucoside now obtained chiefly from buckwheat. It is almost nontoxic and does not accumulate in the body

Griffith and Lindauer were the first to use rutin extensively and have had far greater experience with it than most investigators Animal experiments suggest that rutin opposes abnormal increases in capillary permeability following histamine and the increased fragility following irradiation although even this has been controverted

capacity and malignant hypertension Rather, we would consider the information given by measurement of Tm_{PAH} an indication of the extent of irreparable vascular damage

The treatment requires hospitalization The least dose of pyrogen is given intravenously which will elicit a daily fever of 101-102 F Tolerance may develop as treatment continues It is met by carefully graded increments in dosage Excessive tolerance may require interruption of treatment for three to five days Treatment is continued for weeks or months until a maximal response has been obtained The response to cessation of the injections is then observed and recurrence of evidences of severe hypertension requires repetition and prolongation of treatment

Time expense, the rigorous nature of the treatment and the possibility of a good outcome must all be evaluated before this regime is undertaken The need for controlled observation in a hospital for minimal periods of two to six weeks is evident The whole must be balanced against the fatal issue of uncontrolled malignant hypertension Some of the discomfort incident to treatment can be controlled by use of aminopyrine or aspirin The renal hemodynamic response to pyrogen is not dependent on fever as such However constant use of antipyretics obliterates the fever curve which is one of the most satisfactory indices of the adequacy of dosage Once a remission has been secured and the rapid progress of hypertension temporarily arrested further treatment by diet or by sympathectomy should be considered

The full mechanism of the response of hypertension to pyrogens is obscure It probably involves not only the immediate hemodynamic responses but profound changes in adrenal cortical function plasma and tissue enzyme systems and the whole body metabolism The nature of the response is under study Until it is understood pyrogen treatment is one of the empiric and if you like nonspecific but effective and lifesaving means of controlling hypertensive disease

IV RUTIN

In 1936 Szent-Gyorgyi proposed the name vitamin P for a substance or group of substances present in paprika and lemon peel believed to restore increased capillary permeability to normal This was the beginning of interest in substances of the general nature of flavone glucosides now widely used clinically in all manner of diseases

The true value of vitamin P like flavones has never been accurately determined, principally because increased capillary permeability has no cleancut clinical equivalent. The terms capillary permeability resistance and fragility have been neither accurately defined nor measured, although they are used confidently by many clinicians For this reason much that has been written and this applies chiefly to the unrestrained literature of the drug houses can be accepted only with large reservations

It is still uncertain precisely what substances were responsible for the vitamin P activity of lemon peel or citrin but most evidence suggests it to be hesperidin chalcone Both the clinical and laboratory reports on vitamin P have been unsatisfying and contradictory so that after 12 years little can be said with confidence as to its clinical application

The structural similarity of hesperidin and rutin led Couch to suggest that the latter might be a better source of vitamin P activity than paprika or lemon rind. Rutin is a flavone glucoside now obtained chiefly from buckwheat. It is almost nontoxic and does not accumulate in the body

Griffith and Lindauer were the first to use rutin extensively and have had far greater experience with it than most investigators Animal experiments suggest that rutin opposes abnormal increases in capillary permeability following histamine and the increased fragility following irradiation although even this has been controverted.

Capillary fragility is usually measured by the Gothlin method which consists of a count of the petechiae appearing in the antecubital space of each forearm in a circle 6 cm in diameter after a cuff pressure of 35 mm Hg is applied to the upper arms for 15 minutes Capillary permeability is measured by Griffith by the patent blue method of McMaster When the dye is injected intracutaneously it is absorbed through the lymphatics which makes them visible Lymphatic flow is increased by anything which increases passage of fluid through capillary walls

Griffith found that 19 per cent of 1,600 hypertensive subjects had increased capillary fragility and an additional 11 per cent had increased capillary permeability The only difference between these and hypertensives showing normal capillary response was that, in a 16 month period of study 10 per cent of the group showing capillary disturbance had apoplexy and only 1 9 per cent of the controls This observation has much interest but the exceptionally high apoplexy rate suggests the need for further studies

One of the chief uses for rutin has come from this suggestion that capillary fragility and the occurrence of stroke parallel one another This correlation is unexpected for while pathologists do not agree as to whether strokes are arterial or venous in origin at least the capillaries have not been considered seriously in the genesis of hemorrhage Here is a problem which needs a definitive answer If capillary fragility does in fact reflect likelihood of cerebral hemorrhage an observation of major importance has been made In the normotensive patient there seems to be no such relationship

Retinal hemorrhage seems also to parallel capillary fragility according to Griffith Nine per cent of hypertensive patients with faults of the capillary wall had such hemorrhages while only 2 per cent showed capillary defects in their absence Grouping all patients with retinal hemorrhage without regard to cause 73 per cent had faulty capillary walls Rodriguez and Root noted increased fragility in 40 per cent of unselected diabetics but in practically all

with diabetic retinopathy whether or not hypertension was present Obversely hypertension and increased capillary fragility can exist without retinal damage Thus in diabetics increased capillary fragility is taken as an early sign of vascular disease closely correlated with the development of retinopathy and possibly later with nephrosclerosis Rutin administered in doses of 20–60 mg three times a day to 70 patients with diabetic retinopathy brought fragility to normal Despite this no improvement occurred in the eyegrounds

It is not necessary to detail the negative evidence Suffice it to say that Schweppe Lindberg and Barker found no increase in fragility after thiocyanate therapy Our experience indicates that, in controlled observations routine medical care restores capillary fragility and probably prevents as many strokes as the same care supplemented with rutin Hemorrhages petechial and otherwise may occur in patients with normal capillary fragility thus casting some doubt on the petechial index measurement as a reflection of bleeding tendency Rutin in high doses does not decrease the permeability of the glomerular capillaries in proteinuria induced in rats by administration of bovine albumin

Reluctantly then we are forced on the evidence available to conclude that the value of rutin in the treatment of hypertensives is still in the experimental stage and that its sale and promotion for this purpose is premature

V VITAMIN A

The administration of large doses (100 000 units or more daily) of preparations containing vitamin A has been claimed to be followed by a reduction of arterial pressure and the relief of some of the symptoms of hypertension With Taylor we have not confirmed this observation in a group of patients whose previous response to symptomatic treatment was well established However certain of the patients thus treated showed increased renal blood flow filtration rate and tubular secretory capacity This renal action

of the vitamin or of some substance associated with it was confirmed by Bing in observations on normal dogs Our data indicate that the effect is not due to the vitamin as such, nor to tocopherol, but to some other unstable component of the fish oil concentrates

Thus it does not seem that vitamin A has a place in the treatment of hypertension except possibly in patients who exhibit a disproportionate degree of renal injury Further study is required before any recommendation can justly be made

VI VITAMIN E

Vitamin E activity associated with natural tocopherols has an accepted scientific status in animal nutrition It is possible that vitamin E deficiencies may occur in people receiving what appear to be adequate diets and that the symptoms of the relief and the evidences of its relief will appear very slowly But what the evidences of human deficiency are has not been established

Vitamin E has been advocated largely in Ontario for the relief of a variety of vascular diseases The evidence is profuse and utterly uncontrolled Such competent clinical experience as there is indicates that the claims are not justified Our impression is that vitamin E has no place in the treatment of vascular disease in hypertension

BIBLIOGRAPHY

BARKER M H The blood cyanates in the treatment of hypertension J A M A 106 762 1936

FANSON E KINSEY D AND PALMER R S Potassium sulfocyanate therapy in essential hypertension New England J Med 229 510 1943

FORSTER R E The medical use of thiocyanates in the treatment of arterial hypertension Am J M Sc 206 668 1943

GOLDRING W The management of hypertension Bull New York Acad Med 19 317 1943

GRIFFITH J Q JR AND LINDAUER M A Increased capillary fragility in hypertension Am Heart J 28 758 1944

GROLLMAN A WILLIAMS J R JR AND HARRISON T R Reduction of elevated blood pressure by administration of renal extracts J A M A 115 1169 1940

HINCHLEY J J HINES E A JR AND GHORMLEY R K Osteoporosis occurring during potassium thiocyanate therapy for hypertensive disease Am J M Sc 215 518 1948

KURTZ, C. M. SHAPIRO H H., AND MILLS, C. S. The results of sulphocyanate therapy in hypertension, Am. J M. Sc. 202 3/8 1941
PAGE, I H. HELMER, O M KOHLSTAEDT K. G KEMPF G F GAMBILL, W D AND TAYLOR, R. D The blood pressure reducing property of extracts of kidneys in hypertensive patients and animals, Ann. Int. Med 15 347 1941
RAWSON R. W HERTZ, S AND MEANS J H Thiocyanate goiter in man Ann. Int. Med. 19 829 1943
TAYLOR, R. D CORCORAN A. C. SHRADER, J C. YOUNG, W C. AND PAGE, I H. The effects of large doses of vitamin A concentrate in normal and hypertensive patients, Am. J M. Sc. 06 659 1943
WALD M. H. LINDBERG, H A AND BARKER M. H. The toxic manifestations of the thiocyanates J A. M. A. 112 1120 1939

15 Sympathectomy in Hypertension

SINCE THE introduction of this surgical treatment for hypertension opinion has varied widely both as to the nature of its action and as to its effectiveness From these controversies much information has been gained, not only about the operation and its effects but indirectly about the natural history of the disease Unfortunately, the mechanism by which these denervations influence the course of hypertension is not worked out

Several isolated observations on splanchnicectomy had been made in France and Italy before its extensive use in this country but these preliminary observations carried no serious conviction It was not until Adson and Peet went enthusiastically to work that interest was aroused and careful investigation begun Shortly after Adson and Brown s announcement of the successful outcome of an anterior nerve root resection for hypertension Page and Heuer also undertook a study of the effects of this operation and of supradiaphragmatic splanchnicectomy as performed by Peet About the same time Smithwick began a careful study to determine the extent of denervation necessary to obtain adequate clinical results In these early days feelings ran high as to the place these operations might have in the treatment of hypertension Their easy acceptance of today was bought dearly 15 years ago

Some have raised the question of the specificity of sympathectomies in the treatment of hypertension maintaining that any ma

for surgical procedure or trauma, including such operations as cholecystectomy can do as much to decrease blood pressure as operations on the sympathetic nervous system. The question is still not fully settled since there is an unquestionable although transient antipressor effect of trauma But the weight of evidence is much in favor of the specific effect of sympathectomy One of the most satisfactory proofs is the fact that in two-stage operations the course of hypertension is not greatly altered by the first stage and changes significantly only after the second operation when denervation becomes bilateral Another striking example is the lack of fall of blood pressure after the extensive laminectomy preliminary to anterior nerve root section Cutting the nerve roots weeks or months later results in significant pressure reduction

The varied results obtained by sympathectomy have led to many conflicting reports ranging all the way from cures to complete failure Doubtless indecision has caused much of the confusion which has existed in clinicians minds It may be fairly said that since the surgical technic has been improved and standardized and since the criteria of operability have been more uniform in the various clinics therapeutic results are becoming more uniform and effective

But sympathectomy remains a palliative and is exceptionally if indeed ever curative Whether these operations prolong life remains unproved on strict experimental evidence yet accumulating clinical evidence suggests that they do Still the data leave much to be desired There is wide variation in the method of evaluation Reports vary from 25 to 90 per cent satisfactory results with different types of sympathectomy done at different stages of the disease It must, therefore be recognized that currently it is impossible to compare directly statistical reports of the various series from different clinics A better evaluation is possible by comparing results of different procedures done in the same clinic

Mode of Action of Sympathectomy

It is probably fortunate that sympathectomy for the treatment of hypertension was developed empirically and before hypotheses were advanced to explain it In fact, had it depended on some of these it might never have been practiced

Investigations conducted on dogs with experimental hypertension have unfortunately added little to the knowledge of the effects of the operations in human beings All but the most widespread destruction of the nervous system have little or no lasting effect on the increased blood pressure in renal hypertension in dogs In contrast, patients suffering from chronic pyelonephritis and hypertension *in some of whom the hypertension is primarily renal* are as *much helped by sympathectomy as those with essential hypertension* As Leriche puts it We do not understand Clinical experience does not agree with the experimental demonstration But these comparisons fail to reckon with the differences in organization of the nervous system in dogs and man Another obvious and, as it appears important difference is that men walk upright imposing a wide number of circulatory readjustments on their heart and vessels from all of which dogs are spared

It seems reasonable to suppose that in man the reduction in blood pressure and other beneficial effects are due to a number of different changes in physiology induced by the operation Therefore too great simplification will probably fall short of giving an adequate explanation of its mechanism Without going into the problem deeply it may be of interest to outline some of the current views on the subject

The view has been hazarded that the effects of the operation do not depend on denervation of the vasculature of the abdomen other than that of the kidneys The effect of sympathectomy is attributed to relief of renal ischemia Accordingly renal denervation as such should be fully effective whereas in the small number of

such operations performed on human hypertensives it has had no effect. And in this view renal ischemia should be the cause of *hypertension which in our view it is not* either clinically or experimentally Finally lumbodorsal sympathectomy is only rarely followed by an increase in basal renal blood flow in patients with well established hypertension. Usually the flow is unchanged after an otherwise satisfactory operation. On the other hand the fact that renal blood flow does not ordinarily decrease after sympathectomy when arterial pressure may have fallen indicates that renal resistance must have diminished and the possibility of significant *changes in blood flow and resistance responses during activity or* emotional stress has not been fully explored It has been suggested that the decrease in basal renal resistance establishes a beneficial and specific effect of renal denervation This point of view too is defective in that it ignores the normal autonomy of the renal circulation by which the kidney varies its vascular resistance as arterial pressure changes in order to maintain a nearly normal rate of blood flow Actually our observations on the effects of spinal and caudal anesthesia indicate that the renal vessels of *hypertensive subjects* react much as do those of normal people The only difference and this would be predicted is that most hypertensives maintain a residue of increased afferent resistance which denervation and a drop in pressure do not remove This residual resistance probably reflects afferent arteriolar sclerosis Thus it seems improbable that sympathectomy reduces arterial pressure by specific influence on the mechanism of renal circulation

A large and especially important vascular area is deprived of its vasomotor supply by sympathectomy The splanchnic vasomotor nerves in contrast to the renal vasomotor nerves are normally highly reactive to change in position to ingestion of food and even to mild exercise Especially the assumption of the erect posture places heavy demands on the competence of this circulation. If it were supposed that interruption of the splanchnic visceral inner

vation reduces arterial pressure in the presence of hypertension solely by causing arteriolar vasodilatation or postarteriolar venular and venous dilatation, it would be difficult to explain a prolonged reduction of pressure, since blood volume adjusts rapidly to the space in which it circulates A tendency to such pooling, presumably in the veins is shown by the frequency with which orthostatic hypotension follows successful sympathectomy In this condition, pooling of blood under the effect of gravity results in decreased venous return and decreased cardiac output which is usually not adequately compensated for by increased heart rate This mechanism simply reflects a failure of reflex adjustment consequent on the wide denervation of the splanchnic and renal area

Another related mechanism, presumably concerned with denervation of arteries and arterioles is the inhibition of pressor responses to cold position and to the Valsalva maneuver after sympathectomy Sympathectomy seems to provide a sluice of unconstricted arterial bed into which blood flows so that pressure peaks are damped or obliterated The advantage of such a mechanism in certain patients seems obvious and in Smithwick s view, it is greatest in those whose symptoms suggest impending cerebral accidents and in whom arterial pressure fluctuates widely on stimulation

Both orthostatic hypotension and decreased pressor responsiveness can be mimicked by high spinal anesthesia but neither is an adequate explanation of the decrease in supine blood pressure either after sympathectomy or during the anesthesia We have shown that high spinal and caudal anesthesia can induce in most patients with essential hypertension a decrease in arterial pressure to the normal level and that this decrease is accompanied by an increase of renal blood flow in most and a considerable decrease of renal vascular resistance in all subjects The same type of decrease of pressure and renal resistance can be induced by spinal anesthesia in dogs with renal hypertension whereas these animals do not respond by a decrease in arterial pressure even to the widest sympathectomy There

is therefore an important difference between the effect of spinal anesthesia and that of sympathectomy Orthostatic hypotension de creased reflex responsiveness and even decreased vascular resistance are not adequate explanations of the many possible beneficial effects of sympathectomy in hypertension

✓In searching for other explanations one may lie in the denerva tion of the adrenal medulla which would reduce its output of ad renaline and nor adrenaline This explanation harks back to the pioneering studies of Crile While Freeman Smithwick and White showed that sympathectomy in human beings tends to increase the responsiveness of vascular musculature to adrenaline, the reactions of patients treated by lumbodorsal sympathectomy indicate that in creased responsiveness is more than balanced by decreased output of pressor hormones from the adrenal medulla And, if we admit that adrenal medullary denervation is part of the pattern we find still another corollary Under certain conditions the oversupply of an adrenal-cortical like hormone desoxycorticosterone causes hy pertension and in animals at least arterial disease We and others have shown that the adrenal cortex can be caused to discharge cortical hormone by injection of adrenaline Consequently it may be that adrenal medullary denervation has a secondary effect on the supply of corticoid pressor substances

Another possibility is that the denervation due to splanchnic section inhibits discharges of excitatory sympathin (sympathin E) from the viscera especially from the liver One other physiologic mechanism may contribute to the over all effect of sympathectomy namely the vasodilatation which results from muscular movement. In completely sympathectomized animals struggling is associated with fall in blood pressure which is abolished by curarine Thus ex ercise in partially sympathectomized subjects may initiate dilator impulses which could significantly aid in lowering arterial blood pressure

In brief there is no unitary explanation of the effect of sympa

thectomy It probably involves postural reflexes, neurogenic adaptations, the adrenal cortex and medulla and the liver, as well as perhaps subtler influences Indirect physical or chemical mechanisms resulting from these (the known) hemodynamic effects may in time act to cause a widespread decrease in peripheral resistance and a lowering of arterial pressure (Wilkins *et al*)

The Operations

The four surgical procedures contemporarily employed are (1) supradiaphragmatic splanchnicectomy and ganglionectomy (Peet) (2) subdiaphragmatic splanchnicectomy and ganglionectomy (Adson and Craig) (3) combined supra and infradiaphragmatic ganglionectomy (ninth thoracic to second lumbar) and splanchnicectomy (Smithwick) and (4) total sympathectomy (Grimson)

1 *Supradiaphragmatic splanchnicectomy* —Probably more consecutive operations of the Peet type have been performed than of the others 1 500 in Peet s last report The results reported both by Peet and by a number of others differ among themselves rather widely In considering these reports the first problem is to recognize that they deal with disparate groups of hypertensive patients and groups observed under very different conditions But we do gain the impression that in a considerable proportion of cases a definite and prolonged reduction in blood pressure has occurred Improvement in the general condition in some of these has been remarkable A larger group shows minor improvement According to Peet s statistics 82 per cent exhibited significant lowering of blood pressure a figure higher than usual experience Symptomatic relief was obtained in 86 per cent

While Peet had a large experience with this operation and without doubt exceptional technical facility the documentation of his numerous observations can hardly furnish criteria for selection of patients from a notoriously fluctuant group Other observers

who perform the operation with great dexterity have not had as much success as he had In this connection we pause to pay tribute to the courage imagination and skill of the late Max Peet.

Supradiaphragmatic sympathectomy is not now as widely practiced because it does not provide as wide a denervation of the splanchnic area as is achieved with the Smithwick operation It should be pointed out, however that the problem of the extent of the operation is far from settled and no one knows for sure what area to denervate Ferris and Reiser have pointed the way to a selection of the extent of denervation by observing cold pressor responses during spinal anesthesia Whether or not this response is a guide is not established. But their data support the view that denervation should usually be extensive even including the fourth dorsal ganglion Grimson and also Evans and Bartels have come to the conclusion that many patients are better off when the area of denervation is a wide one

2 *Infradiaphragmatic splanchnicectomy* —This operation was developed at the Mayo Clinic by Craig and Adson. Their results with it are somewhat better than with the supradiaphragmatic operation but they find that only in 13 per cent can results be classified as good and in 18 per cent as fair with regard to reduction of arterial blood pressure Relief of symptoms is striking in a larger percentage of patients

Others have had much the same experience with this operation While it appears possibly to be more effective than supradiaphragmatic sympathectomy the improvement is not sufficient to consider it the one of final choice Most present opinion leans toward abandoning it But a few notably Heinbecker who view the adrenal denervations as the crucial effect of sympathectomy hold to this form of operation

In passing it is well to point out that the various types of operations which have been performed are experimental steps in the

development of the treatment of hypertension by surgery There is sometimes a tendency to be unduly critical because a variety of operations has been tried

3 *Anterior nerve root section*—Anterior nerve root section is an operation first performed by Adson and Brown and carefully studied by the Mayo group and by Page and Heuer The results on the whole are as good as those of the Smithwick operation, but the far greater difficulties and dangers make it an unjustifiable procedure It has now been abandoned but studies on it laid the groundwork for subsequent work in this field

4 *Transdiaphragmatic sympathectomy*—Smithwick has made an extended and carefully planned investigation of the effect on arterial pressure of removing various parts of the autonomic nervous system He found that as the denervation became more complete a significant fall in blood pressure occurred when the patient stood upright He seems to have demonstrated by multiple stage operations that failure to modify the hypertension could be due to inadequate denervation especially since potentially important nerve pathways arise from the sympathetic trunks from the dorsal third to the lumbar third segments At times a failure could be converted into a success by increasing the extent of the denervation But in some cases nearly total sympathectomy failed to modify the hypertension

Finally he hit on the idea of combining both the supra and the infradiaphragmatic approach completing each side in one stage The complete operation interrupts vasoconstrictor impulses to the legs as well as to the entire splanchnic bed The results seem superior to those of other operations

Smithwick reported on 156 patients studied carefully over one to five years He divided the results into five groups (not to be confused with Keith and Wagener's groups) according to the resting horizontal lowering of diastolic pressure after operation The average reduction (systolic/diastolic) was group I 61/45

mm. Hg group II 44/24 group III 27/15 group IV 10/5 In group V the pressure rose on the average 18/11 mm Hg There were 64 patients in group I 32 in group II and 28 in group III Results in groups I and II were considered significant and in group III probably significant. Thus 96 patients almost surely and 28 more possibly were benefited by the operation.

His alternative method of classifying patients by types" is based on estimation of pulse pressure in the resting horizontal posture Patients with narrow pulse pressure which is less than half the diastolic pressure are placed in type 1 Those with wider pulse pressure equal to or up to 19 mm more than half the diastolic pressure constitute type 2 Finally those with pulse pressure 20 mm or more greater than one half the diastolic pressure form type 3 The results of the operation were best in type 1 and poorest in type 3 It is interesting that the best results occurred in type 1 females and poorest in type 3 males

Eleven of the 156 patients had pyelonephritis and in all but one it was bilateral. Smithwick notes that as a group these patients did unusually well Incidentally the surgical exposure used by Smithwick allows careful inspection of the kidneys and adrenal glands This is proving to be important in some hypertensives in whom adrenal tumors are revealed

The effects of operation do not appear to be primarily dependent on the state of the renal arterioles as judged by renal biopsy since there was no significant difference in results in patients with mild or no renal arteriolar disease and those having more advanced changes This is in accord with older studies in which the state of the renal vasculature was estimated indirectly from clearance studies Clearly this fact along with others cited, indicates that the primary effect of radical sympathectomy is not on the renal vascular bed Still it should be recognized that most if not all patients with severe renal disease do not benefit materially from the operation and that they may even suffer damage

5 *'Total sympathectomy'*—Grimson in 1940 performed the first complete sympathectomy for hypertension The evidence he derived from dogs made hypertensive by carotid sinus and aortic depressor nerve section suggested that this procedure might be more beneficial than the less extensive sympathectomies or splanchnicectomies previously performed He removed the sympathetic chains intact in patients down to, and occasionally including the first and second lumbar ganglions

Several patients have shown varying degrees of late incomplete restoration of the preoperative blood pressure level and a few an additional late lowering of blood pressure Response to the cold pressor test is depressed for a few weeks after the most complete sympathectomies Later, the response returns to levels observed before operation The diminished heart rate due to cardiac denervation apparently persists rates between 40 and 60 being frequent Postural lowering of blood pressure was observed in all patients and tends to persist Most showed significant and persistent reduction of arterial pressure when measured in the supine posture

Grimson believes the advantages of this procedure over the less extensive sympathectomies are a more consistent lowering of blood pressure a slow regular heart rate postural hypotension without tachycardia and probably decreased likelihood of sympathetic regeneration The disadvantages not all limited to total sympathectomy are greater operative morbidity and mortality decreased vital capacity difficult postoperative management bilateral Horners syndrome occasional chronic nasal congestion excessive sweating in patches occasional prolonged weakness and postural disability more extensive postoperative pain and psychic trauma and in an occasional male patient decreased fertility

Urea clearance decreased slightly immediately after total sympathectomy but in six months to a year often reached or exceeded its preoperative level This operation must still be considered experimental

SELECTION OF PATIENTS FOR SYMPATHECTOMY

Many have been the attempts to find a single test or even a group of tests which will yield reliable information as to whether or not sympathectomy will favorably influence hypertension Certainly no single test has been found satisfactory Gradually most investigators are becoming agreed that certain observations are necessary before even rough forecasting is possible

Patients over age 55 are usually rejected as are those with cardiac failure who do not respond to treatment or those with extensive cerebral arteriosclerosis and repeated strokes Arrhythmias such as auricular fibrillation, flutter or block contraindicate operation while they persist and are not adequately controlled. As Fishberg points out symptoms due to arteriosclerosis will not be helped and may be aggravated by sympathectomy which explains Smithwick s aversion to operating on all patients with high pulse pressure In contrast to patients with advanced renal or cerebral disease many with cardiac compensation who respond to medical treatment often do surprisingly well after operation Even moderate reduction of the load on the heart may prevent further episodes of decompensation for several years

The best results are certainly obtained in Keith and Wagener s or Smithwick s groups I and II The gamble becomes greater with group III and is further increased in group IV

The most striking and least disputed effects of sympathectomy as we pointed out 12 years ago occur in some patients with full blown early malignant hypertension At that time most surgeons believed the malignant syndrome to be a definite contraindication for surgery and some still share this view However enough of these patients have now been subjected to operation in a number of clinics with moderately good results to justify the risks involved It is of course not surprising that operative mortality is greatest among these patients Still one of the most dramatic ex

periences in the treatment of hypertension is to see the rapid subsidence of the retinopathy and the disappearance of headache and congestive failure While a few hypertensives who enter this malignant phase have spontaneous remissions, most of them do not. *At least 90 per cent will die within two years of the onset of signs* of accelerated vascular disease

Unfortunately, not all of the good results are lasting But many

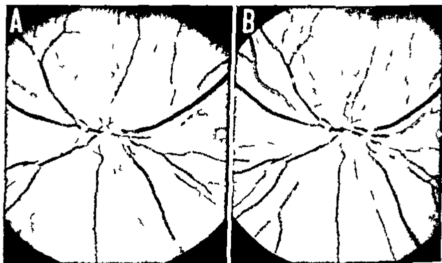


FIG 16—Eyegrounds of patient with malignant hypertension *A* before and *B* after sympathectomy The disappearance of papilledema and edema of the retina is clearly portrayed Constriction of arterioles seems to have lessened to some extent

of our patients have so long outlived what could reasonably be expected as to leave little doubt in our minds that operation prolonged their lives The increased life expectancy is perhaps most clearly shown in a mortality survey by Peet and Isberg They noted that 19 per cent of 112 such patients are living five to 11 years later If the operation is performed early in the course of the disease and renal function is good the chances of success are improved and the value of the operation most clearly seen How

ever we believe that except for research purposes operation should not be performed unless there is evidence of progressive vascular deterioration Whether sympathectomy will prevent vascular deterioration when performed very early before it has appeared is not yet known

There is a difference of opinion whether or not renal damage is a contraindication to operation and, granting it is how much damage is significant. Certainly moderate degree of loss of renal efficiency i e ability to concentrate urine to a specific gravity of 1 018–1 022 is not sufficient grounds to refuse operation. But the more severe grades with reduction of urea clearance below 50 per cent of normal and deterioration of concentrating power to 1 010 or 1 012 interdict it. Here it is important to be sure that the failure is renal and not due to remediable cardiac failure It has been our impression that the *rate* of loss of renal efficiency is as important as the amount lost Urea clearance and concentrating ability that are low and falling rapidly constitute an almost certain contraindication. Since renal function is not appreciably altered as a direct effect of sympathectomy there need be no fear that uremia will be precipitated by transitory postoperative collapse which is adequately treated.

The average level of the blood pressure is not a good index of the result to be expected from operation When diastolic pressure is excessively high a less favorable result may be expected, but this is no more than saying that the operation is less effective as the disease is more severe It is an impression that the more labile the pressure the better the result This is possibly true but again should not be made too important a factor in the decision Smithwick s use of pulse pressure as an index may prove more valuable than average arterial pressure possibly because it aids in excluding patients with arteriosclerotic hypertension. However it is his impression that the demonstration of a hyperreactive pressor mechanism is an important guide even when basal blood pressures are normal

or nearly so One test of this, which seems to us more critical than a cold pressor test can ever be, *is the observation of the pressure* overshoot after a Valsalva maneuver The patient breathes out against a resistance of 40 mm Hg for 10 seconds during which pressure transitorily falls Normally there should be little rise of pressure beyond control levels in the succeeding 15–120 seconds Many hypertensive patients show large overshoots at this time These overshoots indicate a vasomotor hyperresponsiveness especially *common in people who later develop strokes, they can be* temporarily abolished or minimized by sympathectomy

Patients with many symptoms such as headache precordial pain feeling of tension and irritability and poor appetite are often benefited strikingly These are significant factors and should not be underestimated On the other hand patients whose symptoms seem to be related more to emotional instability than to vascular disease *are sometimes only made worse*

An important issue is whether the patient is a good sport and given to taking a hopeful outlook While these considerations do not determine the outcome they go far to lessen the disappointment of a failure

Laboratory tests have given no decisive answer to the problem of selection Possibly one of the best is Allen and Adson s sodium *amytal*[8] *test Three grains of this drug is given* every hour for three hours i e 9 gr and the blood pressure is measured during this period *If* the diastolic pressure decreases to less than 110 mm Hg good or fair results occur almost four times as frequently as when the arterial pressure does not fall below 120 mm Hg But there are many examples of results which were eventually poor despite adequate response of the diastolic pressure Allen finds it easier to be accurate in the prediction of poor results than of good ones

Other tests have been proposed such as administration of 1½ gr sodium nitrite each hour for six hours intravenous injection of

pentothal sodium* or tetraethylammonium and induction of spinal anesthesia, but they appear to have no advantage over the simple test proposed by Allen and Adson The cold pressor test also does not appear to have any prognostic value in relation to operation. Thus despite the multiplicity of tests which have been suggested, none of them have proved worth The Valsalva test has perhaps as much or more to commend it than any other At least, it is con cerned with simple hemodynamic changes and does not involve the many mechanisms which enter even into the cold pressor test.

Thus the selection of patients for sympathectomy is still in the empiric stage Those most experienced and successful in this procedure use a combination of the factors listed, along with a large flavoring of intuition. Such experienced surgeons do surprisingly well in their forecasting But the lists of indications and contra indications written by many surgeons show no consistency and for the most part are only statements of opinion

It is difficult to phrase a statement of indications for sympa thectomy They are to our view as follows (1) age less than 55 and physiologic age more significant than chronological (2) ad vancing vascular disease uncontrollable by other means (3) oc casional severely hyperreactive patients (cold pressor Valsalva, emotion) who have shown symptoms of impending cerebral disease and (4) early malignant hypertension

Miscellaneous Considerations

Patients with very early and labile hypertension especially women are more and more being subjected to operation with the hope that the progress of the disease will be stopped before an irreversible phase has been reached So it is not surprising that many reports that show the most impressive benefits are those of operations on women with early hypertension The best results should be expected in this group (1) because hypertension in women is often benign (2) *it is often* very labile, and (3) women

achieve at least a temporary reprieve from the ravages of the disease and their life span is increased Often what span of life remains becomes far more bearable No especial benefit occurs to the kidneys, and severe renal injury is a contraindication The heart may be benefited by relief from some of its load The cerebral vessels can only indirectly be aided

Thus if the circumstances are suitable, there can be little doubt that an adequate sympathectomy is often followed by significant therapeutic results But the suitability of the circumstances is not always easy to determine Our experience in patients with advancing vascular disease indicates after three years, roughly 15 per cent apparent cures, another 25 per cent symptomatically and objectively improved, 25 per cent symptomatically better and the remainder unchanged

BIBLIOGRAPHY

ALLEN E V AND ADSON A W Physiologic effects of extensive sympathectomy for essential hypertension Further observations Ann Int Med 11 2151 1938

——— The treatment of hypertension Medical versus surgical Ann Int Med 14 288 1940

CORCORAN A C AND PAGE I H Renal blood flow and sympathectomy in hypertension Arch Surg 42 1072 1941

DE TAKATS G GRAUPNER G W FOWLER E F AND JENSIK R J Surgical approach to hypertension Arch Surg 53 111 1946

EVANS J A AND BARTELS E C Results of high dorsolumbar sympathectomy for hypertension Ann Int Med 30 291 1949

FISHBERG A M Sympathectomy for essential hypertension J A M A. 137 666 1948

FREEMAN N E SMITHWICK R. H AND WHITE J C Adrenal secretion in man The reactions of the blood vessels of the human extremity sensitized by sympathectomy to adrenalin* and to adrenal secretion resulting from insulin hypoglycemia Am J Physiol 107 529 1934

GRIMSON K S The surgical treatment of hypertension Collective review Surg Gynec & Obst 75 421 1942

HINTON J W End results of thoracolumbar sympathectomy for advanced essential hypertension Bull New York Acad Med 24 239 1948

LORD J W JR AND HINTON J W The operative and postoperative management of hypertensive patients undergoing thoracolumbar sympathectomy New England J Med 237 840 1947

PAGE I H AND HEUER C J The effect of splanchnic nerve resection on patients suffering from hypertension Am J M Sc 193 820 1937

——— Treatment of essential and malignant hypertension by section of anterior nerve roots Arch Int Med 59 245 1937

——— Medical aspects of surgical treatment of hypertension J. A. M. A. 110 1161 1938

——— The effect of renal denervation on the level of arterial blood pressure and renal function in essential hypertension J. Clin. Investigation 14 27 1935

PALMER, R. S NYSSENS A. F., AND WHITE, J. C. Severe hypertension with papilledema simulating brain tumor Differential diagnosis and treatment New England J. Med 239 322 1948

PEET M. M. Hypertension and its surgical treatment by bilateral supradiaphragmatic splanchnicectomy Am. J Surg. 75 48 1948

——— WOODS W W AND BRADEN S The surgical treatment of hypertension Results in 350 consecutive cases treated by bilateral supradiaphragmatic sympathectomy and lower dorsal sympathetic ganglionectomy J. A. M. A. 115 1875 1940

——— AND ISBERG E. M. The surgical treatment of essential hypertension J. A. M. A. 130 467 1946

SMITHWICK, R. H *Surgery of the autonomic nervous system* New England J. Med. 236 662 1947

WHITE, J. C., AND SMITHWICK, R. H The Autonomic Nervous System (2d ed New York The Macmillan Company 1941)

WILKINS, R. W CULBERTSON J W AND HALPERIN M. H. The hemodynamic effects of sympathectomy in essential hypertension Ann. Int. Med. 30 291 1949

16 Diet in the Treatment of Hypertension

DIETARY TREATMENT is always fascinating and popular People *instinctively feel that a change in diet might be helpful* Thus for most common diseases almost the whole gamut of possible changes has been made and almost every one has been touted as the one sure cure In retrospect one fact seems certain severe changes in man's normal diet must be made with care This is not to say that carefully studied changes are not of proved value For example a sodium poor diet creates a negative sodium balance which helps rid the body of edema Such a diet is therefore recommended in congestive failure and other conditions in which sodium is abnormally retained But this does not imply that we should all use diets deficient in sodium or in other factors mineral or organic

The warning of history that diets should be varied from the normal only with great circumspection is especially applicable in treatment of essential hypertension Here the situation is very different from the immediacies of congestive failure acute nephritis and similar states for any effective treatment may have to be continued for years Time is thus allowed for the unforeseen deleterious effects of an inadequate diet to manifest themselves Clearly then since excessively low sodium and rice diets are both highly abnormal their long term effects are unknown and their use must

be considered experimental until these effects can be evaluated.

It is unnecessary to recount the many attempts to lower arterial pressure by diet. Current practices are largely refinements of older ones which in no small measure accounts for the fact that diets now in use must be much more rigidly controlled than the older ones and for much of the controversy which remains. Thus low salt diets have been used in cardiovascular disease for at least 40 years Only recently has the requirement been set that the urinary excretion of sodium be 200 mg or less in 24 hours for the dietary control to be considered effective Whether such rigid restriction is always necessary is another question. The point we wish to stress is that salt poor diets may differ widely so that what was a salt poor diet a decade ago would be almost salt rich under current standards

Low Sodium Diets in Hypertension

At this point a sharp distinction must be made between the use of low sodium diets in the treatment of the cardiac failure in hyper tension and in the compensated phase of the disease The usefulness of these diets in the former is not in doubt the uncertainty con cerns the treatment of hypertension as such. Ambard in France Volhard in Germany and Allen in the United States long ago rec ommended *chloride and sodium restriction in the treatment of compensated hypertension*. Allen and Volhard s studies in particular were well carried out but the work received only scant confirma tion particularly when the moderate salt restriction they used was practiced

Kempner s work on rice diets and Grollman s re study of the low sodium diet problem have brought renewed interest and ex tensive use of both diets We shall consider at this point only the drastic low sodium diets of the sort used by Grollman These should be considered experimental and not recommended *for routine treat* ment of patients for it is far from proved that these diets have

16 Diet in the Treatment of Hypertension

DIETARY TREATMENT is always fascinating and popular People instinctively feel that a change in diet might be helpful Thus, for most common diseases almost the whole gamut of possible changes has been made and almost every one has been touted as the one sure cure In retrospect one fact seems certain severe changes in man s normal diet must be made with care This is not to say that carefully studied changes are not of proved value For example a sodium poor diet creates a negative sodium balance which helps rid the body of edema Such a diet is therefore recommended in congestive failure and other conditions in which sodium is abnormally retained But this does not imply that we should *all* use diets deficient in sodium or in other factors mineral or organic

The warning of history that diets should be varied from the normal only with great circumspection is especially applicable in treatment of essential hypertension Here the situation is very different from the immediacies of congestive failure acute nephritis and similar states for any effective treatment may have to be continued for years Time is thus allowed for the unforeseen deleterious effects of an inadequate diet to manifest themselves Clearly then since excessively low sodium and rice diets are both highly abnormal, their long term effects are unknown and their use must

Clearly this is not an easy regime to follow Unless adhered to scrupulously it certainly will have no value and will be a needless nuisance and expense Even if it is followed with care there is no assurance that it will do good Unless the physician can and will carefully study his patient, the diet should not be used. While there are scattered reports of great success with these diets almost none of them bear thorough scrutiny It is now recognized that what effects are achieved seem to be associated with the sodium rather than with the chloride deprivation In some patients sodium deprivation is assisted by prescribing ammonium chloride (1 Gm 15 gr) three times daily for three days in the week.

Since the aim of a low sodium diet is sodium depletion the logic of treatment suggests that depletion be hastened in certain patients by the use of mercurial diuretics as well as ammonium chloride Such rapid desalting has the advantage of indicating in short order the probability of a long term response to treatment by diet Megibow and co-workers have suggested injection of mercupurin 2 cc intramuscularly at intervals of one to four days after starting a low sodium diet. Since such a regime increases somewhat the hazards of sodium restriction it should be reserved for patients who are under careful supervision and control

Dangers of drastic sodium restriction —It must be obvious that such drastic sodium restriction is not without danger Most people know that in hot climates vascular collapse can occur when sweating and loss of salt are excessive and can be in part alleviated by taking salt It is possible that the lowering of blood pressure in some hypertensive patients when it occurs is a milder form of this vascular collapse seen in normal persons under the stress of salt-water loss due to heat In short the patient must live in the narrow range where salt withdrawal is sufficient partially to lower blood pressure but insufficient to precipitate collapse

When the kidneys are functioning normally the zone in which the body can safely operate is reasonably wide But with damaged

long term value in the treatment of hypertension There is no doubt that many patients do not respond at all Further, no test has been devised for the selection of those who will respond

Preparation of low sodium diets (Appendix 3) —One of the chief problems of physicians wishing to give the drastic low salt diet is its preparation and the preparation of the patient to take it These diets usually are monotonous and tasteless They should be cooked with care, for Can that which is unsavory be eaten without salt? (Job 6 6) Some people simply refuse to eat them others discontinue them after several weeks Many others find it practically impossible to prepare the diet or to have it prepared for them in a palatable way Even with intelligent patients constant control is necessary lest some unforeseen source of sodium be admitted to this socially select group of dietary molecules Treated as out patients it is safe to say that few patients will be able to keep the sodium intake below 200 mg daily

Certain rules for guidance may be useful (1) The problem must be presented to the patient fairly and be thoroughly understood by him An alternative is to hector or bully him into submission (2) Food must be individually prepared without salt Helpful friends and relatives should be discouraged from aiding in the diet (3) *A reliable list of low sodium foods must be adhered to* such as the one on page 386 Specially prepared sodium poor milk powder (Ionalac®—Mead Johnson and Company) has proved a useful part of the diet (4) Seasoning should be used whenever desired being sure the seasoning is sodium free and as we now know lithium free There is probably no harm in use of potassium containing salt substitutes in the absence of uremia and oliguria The meal should be served attractively (5) The 24 hour urinary chloride or better sodium should be occasionally determined and the patient informed of the result This is the final control of the adequacy of the diet The 24 hour specimen should not contain more than 200 mg of sodium

Clearly this is not an easy regime to follow Unless adhered to scrupulously it certainly will have no value and will be a needless nuisance and expense Even if it is followed with care there is no assurance that it will do good Unless the physician can and will carefully study his patient the diet should not be used. While there are scattered reports of great success with these diets, almost none of them bear thorough scrutiny It is now recognized that what effects are achieved seem to be associated with the sodium rather than with the chloride deprivation In some patients sodium deprivation is assisted by prescribing ammonium chloride (1 Gm. 15 gr) three times daily for three days in the week.

Since the aim of a low sodium diet is sodium depletion the logic of treatment suggests that depletion be hastened in certain patients by the use of mercurial diuretics as well as ammonium chloride Such rapid desalting has the advantage of indicating in short order the probability of a long term response to treatment by diet Megibow and co-workers have suggested injection of mercupurin[*] 2 cc intramuscularly at intervals of one to four days after starting a low sodium diet. Since such a regime increases somewhat the hazards of sodium restriction it should be reserved for patients who are under careful supervision and control

Dangers of drastic sodium restriction—It must be obvious that such drastic sodium restriction is not without danger Most people know that in hot climates vascular collapse can occur when sweating and loss of salt are excessive and can be in part alleviated by taking salt It is possible that the lowering of blood pressure in some hypertensive patients when it occurs is a milder form of this vascular collapse seen in normal persons under the stress of salt-water loss due to heat In short the patient must live in the narrow range where salt withdrawal is sufficient partially to lower blood pressure but insufficient to precipitate collapse

When the kidneys are functioning normally the zone in which the body can safely operate is reasonably wide But with damaged

function the picture is different As salt is withdrawn in normal people it quickly disappears from the urine and the loss from body water halts Plasma sodium maintains itself at relative constancy In contrast, patients with damaged kidneys or those under treatment with mercurials do not show this remarkable conservation phenomenon Day after day almost undiminished amounts of sodium appear in the urine and water continues to be lost from the body The kidneys are unable to stop the losses until oligemia and hyponatremia result in vascular collapse This phenomenon is well known in the terminal phase of glomerulonephritis when misguided treatment demands rigid salt restriction in the face of isosthenuria

While administration of salt will cure these acute episodes the cure is sometimes not as rapid as might be expected Even with *large amounts of salt, from 12 to 24 hours may be required before* the disturbances set up are remedied

Renal blood flow may fall during drastic sodium restriction and ability to concentrate urine may decrease Within the year or more that this has been studied it appears to be a reversible process On the other hand if the reduction is of sufficient degree and its cause unrecognized great damage might be inflicted This problem deserves careful consideration before these diets are widely used A few patients show increased cylindruria during low sodium treatment

We hope that we have made it clear that the drastic low sodium diets are distinctly experimental Only a few patients appear to respond with a significant fall in blood pressure and no means are known for selecting those who will respond The diet is difficult to prepare and costly It is not without danger on two counts (1) vascular collapse from extreme salt deprivation is always just around the corner and (2) renal efficiency is often temporarily significantly reduced Study of these diets is however well justified and it is hoped that those in a position to investigate them adequately will do so with care and dispatch

The Kempner Rice Diet

Few suggestions for the treatment of hypertension have so stirred controversy as the rice diet. Every shade of opinion exists Some see in it a cure while others view it as deserving of nothing more than casual interest. At present it is not possible on the basis of published evidence to arrive at any considered opinion of its value Many of us remember the extremes of view expressed 15 years ago about sympathectomy This emotional approach as one looks back on it, contributed little to understanding of the nature of the problem

The rice diet and the sodium depletion diet are alike in that each yields about 2 000 calories fuel value and contains less than 0 5 Gm of sodium They differ in their protein content, which in Kempner s regime is less than 20 Gm. and also in Kempner s assumption that other foods contain unidentified toxic substances not present in rice which embarrass the kidneys

Are the effects of the diet due to its low salt content to its low vegetable protein content, to loss of weight, to negative nitrogen balance or to a combination of these plus aggressive mass psychotherapy? The answer is certainly that we do not know In our hands the few patients who show a consistent decrease in pressure on the rice diet show the same change on a low sodium diet, and the decrease in both cases is abolished by giving sodium chloride Many of these problems will soon be answered. The only danger is that, meanwhile powers may be unconsciously conferred on a diet with a catchy name whose value has yet to be even empirically proved. Thorough study is certainly justified but its importance must be kept in focus with other aspects of experimental therapy

We may be allowed two observations, which we confess have been made a good many times before more detailed discussion of the diet First, and important, Kempner like many enthusiastic

clinicians, from his reports does not seem to evaluate the hypertensive patient's condition adequately in a control period before the diet is started This is a serious criticism and one repeatedly leveled at surgeons with only sporadic success At the very least three weeks and often several months are required before even a semblance of a control base line can be established, and in some patients even this is not enough

In 1944 Kempner first reported on the use of the rice diet It contains 2 000 calories, not more than 5 Gm fat, 20 Gm protein, 200 mg chloride and 150 mg sodium From 250 to 350 Gm of rice (dry weight) is taken daily All fruits are allowed except nuts dates avocados and dried or canned fruit or fruit derivatives to which substances other than white sugar have been added Not more than one banana a day may be taken White sugar and dextrose are allowed *ad libitum*, on the average a patient takes about 100 Gm daily but, if necessary, as much as 500 Gm may be used Tomato and vegetable juices are not allowed Usually no water is given and the daily fluid intake is limited to 700–1 000 cc of fruit juice Supplementary vitamins are added—vitamin A 5 000 units D 1 000 units thiamine hydrochloride 5 mg riboflavin 5 mg, niacinamide 25 mg calcium pantothenate 2 mg Rest in bed is neither necessary nor desirable Weight may decrease markedly during the first 20 days

The diet should be continued without modification until the conditions which were the indication for its use have disappeared Then small amounts of nonleguminous vegetables potatoes lean meat or fish (prepared without salt or fat) may be added

Nitrogen equilibrium is said by Kempner to be maintained despite the low protein content although Schwartz and Merlis found excretion of nitrogen greater than the intake i e a negative balance Blood nonprotein nitrogen was lower in patients on the rice diet than in normal or fasting persons (i e 27 compared with 34 mg) and average urea nitrogen was 14 1 mg before the diet and

7.8 mg after Hypercholesteremia decreased markedly with the rice diet. In 200 of 284 patients with hypertensive vascular disease (70 per cent) who had cholesterol concentrations of at least 220 mg per 100 cc 132 exhibited a decrease to normal levels Free cholesterol and cholesterol esters decreased during the rice regime in about the same proportion. There was a decrease of 99 per cent in sodium concentration in the urine and of 4 3 per cent in blood and an insignificant increase in potassium concentration.

Kempner's indications consist of all serious instances of acute and chronic nephritis heart failure which does not respond to the customary salt restriction and drugs arteriosclerotic and hypertensive vascular disease with cardiac cerebral retinal or renal involvement and uncomplicated hypertensive vascular disease when a more liberal regime weight adjustment restriction of activities sedatives etc have failed. It is suggested as a therapeutic test before sympathectomy is considered.

In cases complicated by peptic ulcer raw fruit should be avoided and only cooked strained fruit used. Water or dialyzed milk may be substituted for the fruit juices There is no contraindication in diabetes mellitus Blood and urine must be frequently checked because loss of Cl and Na may reach serious proportions Sodium cannot be replaced as quickly as might be supposed after depletion

Symptomatic improvement may be striking Of 500 patients most of whom were seriously ill and many of whom had according to Kempner failed to respond to other forms of treatment, the diet was ineffective in 178 In 322 it produced one or more of the following changes decrease in mean blood pressure of at least 20 mm Hg reduction of heart size by 18 per cent or more change in T_1 from completely inverted to upright, disappearance of severe retinopathy The time required for the blood pressure to decrease varied from four days to 10 months In 40 with and 85 without renal involvement, blood pressure returned to normal or almost

clinicians, from his reports does not seem to evaluate the hypertensive patient's condition adequately in a control period before the diet is started This is a serious criticism and one repeatedly leveled at surgeons with only sporadic success At the very least, three weeks and often several months, are required before even a semblance of a control base line can be established and in some patients even this is not enough

In 1944, Kempner first reported on the use of the rice diet It contains 2 000 calories not more than 5 Gm fat, 20 Gm protein 200 mg chloride and 150 mg sodium From 250 to 350 Gm of rice (dry weight) is taken daily All fruits are allowed except nuts dates avocados and dried or canned fruit or fruit derivatives to which substances other than white sugar have been added Not more than one banana a day may be taken White sugar and dextrose are allowed *ad libitum*, on the average a patient takes about 100 Gm daily but if necessary, as much as 500 Gm may be used Tomato and vegetable juices are not allowed Usually no water is given and the daily fluid intake is limited to 700–1 000 cc of fruit juice Supplementary vitamins are added—vitamin A, 5 000 units D 1 000 units thiamine hydrochloride 5 mg riboflavin 5 mg niacinamide 25 mg, calcium pantothenate 2 mg Rest in bed is neither necessary nor desirable Weight may decrease markedly during the first 20 days

The diet should be continued without modification until the conditions which were the indication for its use have disappeared Then small amounts of nonleguminous vegetables potatoes lean meat or fish (prepared without salt or fat) may be added

Nitrogen equilibrium is said by Kempner to be maintained despite the low protein content, although Schwartz and Merlis found excretion of nitrogen greater than the intake i e a negative balance Blood nonprotein nitrogen was lower in patients on the rice diet than in normal or fasting persons (i e 27 compared with 34 mg) and average urea nitrogen was 14 1 mg before the diet and

LANDOWNE, M. The low sodium diet in vascular diseases, J Am. Dietet. A. 24 187 1948
MEGIBOW R. S POLLACK, H. STOLLERMAN G H. ROSTON E. H., AND BOOKMAN J J The treatment of hypertension by accelerated sodium depletion J Mt. Sinai Hosp 15 233 1948
PAGE, I H CORCORAN A. C. AND TAYLOR, R. D Diet in the treatment of hypertensive disease Postgrad. Med. 5 211 1949
PERERA, G A. AND BLOOD D W The relationship of sodium chloride to hypertension, J Clin. Investigation 26 1109 1947
VIERSMA, H J Therapy of Hypertension with Salt Free Diets and with Elimination of Salt (Amsterdam, 1945)

normal values Of 406 patients with diastolic pressures over 100 mm Hg blood pressure decreased from 1 to 62 mm average 18 mm in 96 per cent, only 4 per cent showed an increase The pressures on the rice diet may be far lower than the lowest value reached by the sodium amytal* test of vascular lability

In 95 per cent of 286 patients the heart became smaller in an average of 118 days In 99 of 310 patients T_1 was completely inverted and in 30 of these it became upright In none did the reverse occur Vascular retinopathy, papilledema, hemorrhage and exudate present in 140 of 500 patients disappeared during the rice diet but retinal improvement did not necessarily coincide with decrease in blood pressure Severe retinopathy often disappeared when blood pressure remained at a constantly high level An average of 14 months was required for retinal changes to disappear completely

Our experience with the rice diet has been that some patients would not stay on the diet because of its monotony Among those who did so after a prolonged control period results have not been impressive In some patients a fall in renal blood flow occurred which so far has seemed reversible The eyegrounds of one patient may have cleared as the result of the diet but this is uncertain for a variety of reasons Several patients all with reduced renal function suffered serious collapse with rising blood urea and reduced carbon dioxide combining capacity while on the diet The syndrome is reversible by administration of a salt containing diet which quickly restores the patients to their former state

BIBLIOGRAPHY

GOLDRING W Consideration of human hypertension with respect to its renal origin and therapy *Am J Med* 4 875 1948

GROLLMAN A HARRISON T R MASON M F BAXTER J CRAMPTON J AND REICHMANN F Sodium restriction in diet for hypertension *J A M A* 129 533 1945

KEMPNER W Treatment of hypertensive vascular disease with rice diet *Am J Med* 4 545 1948

facilities for refrigeration are inadequate the bottle is rinsed with a few drops of formalin* or tricresol He is instructed to take no fluid no fruits nothing such as gelatin desserts or ice cream which in some phase of its existence can be poured This restriction is to begin at 8 A M on the day of the test and to continue until 8 A M the following day He is to discard urine passed during the day and to void and discard urine at 8 P M All urine passed after 8 P M is collected in the bottle including the specimen passed at 8 A.M. on the second day The urine is then brought for examination Undue thirst may be relieved by chewing gum.

PROCEDURES

Estimation of concentrating power—1 The temperature of the urine specimen is measured and specific gravity found with an accurate (tested and checked) urinometer It is important to avoid parallax in taking the reading and to insert the urinometer into the urine with a spinning motion so that it is freely floating in the cylinder Most urinometers are calibrated against water at 15 C. Consequently the observed reading is corrected for the temperature of the specimen by adding 0 001 for each 3 degrees above 15 C. or by subtracting this amount for lower temperatures

2 Urine pH is then measured with nitrazine test paper

3 Urinary glucose is searched for (quantitative Benedict's reagent) or estimated semiquantitatively using one of the office test kits (e g Clinitest)

4 URINARY PROTEIN This is measured by the method of Addis and Shevky

Principle Protein is precipitated by addition of an alcoholic solution of phosphotungstic acid and the precipitate is packed to a measured volume in the calibrated narrow stem of a special centrifuge tube under standard conditions

Method. To 4 cc of filtered or clear normal or slightly proteinuric urine or to the same volume of a water dilution (1/4 1/10 1/20) of heavily proteinuric urine in an Addis-Shevky tube add

Appendix 1 METHODS OF FUNCTIONAL EXAMINATION OF THE KIDNEY

I ADDIS TEST ESTIMATION OF CONCENTRATING POWER SEDIMENT COUNT

APPLICATION Detection and estimation of early stages of renal damage The concentration test is contraindicated in renal failure with azotemia Since concentrating power has already been lost in most such cases the test serves no purpose and water deprivation may intensify the condition The sediment count can be done at any stage of the disease

PRINCIPLE Deprivation of water during a period of normal solid intake increases the osmotic pressure of body fluids This change stimulates the posterior pituitary to release antidiuretic hormone The extent to which the cells of the distal convoluted tubules respond to the hormone measures their capacity for osmotic work This osmotic work consists in reabsorbing hypotonic fluid from the distal tubule against the pull of the residual hypertonic urine

COLLECTION OF URINE

Urine is collected during the last 12 hr of a 24 hr dry period The specific gravity is measured and corrected for protein content The specimen is also used for estimation of protein output in the urine and for the sediment count

The patient is given a clean dry bottle such as a Mason jar If

facilities for refrigeration are inadequate the bottle is rinsed with a few drops of formalin* or tricresol He is instructed to take no fluid, no fruits nothing such as gelatin desserts or ice cream, which in some phase of its existence can be poured. This restriction is to begin at 8 A.M on the day of the test and to continue until 8 A M the following day He is to discard urine passed during the day and to void and discard urine at 8 P M All urine passed after 8 P M is collected in the bottle including the specimen passed at 8 A.M. on the second day The urine is then brought for examination Undue thirst may be relieved by chewing gum.

PROCEDURES

Estimation of concentrating power—1 The temperature of the urine specimen is measured and specific gravity found with an accurate (tested and checked) urinometer It is important to avoid parallax in taking the reading and to insert the urinometer into the urine with a spinning motion so that it is freely floating in the cylinder Most urinometers are calibrated against water at 15 C. Consequently the observed reading is corrected for the temperature of the specimen by adding 0 001 for each 3 degrees above 15 C. or by subtracting this amount for lower temperatures

2 Urine pH is then measured with nitrazine test paper

3 Urinary glucose is searched for (quantitative Benedict s reagent) or estimated semiquantitatively using one of the office test kits (e g Clinitest)

4 URINARY PROTEIN This is measured by the method of Addis and Shevky

Principle Protein is precipitated by addition of an alcoholic solution of phosphotungstic acid and the precipitate is packed to a measured volume in the calibrated narrow stem of a special centrifuge tube under standard conditions

Method. To 4 cc of filtered or clear normal or slightly proteinuric urine or to the same volume of a water dilution (1/4 1/10 1/20) of heavily proteinuric urine in an Addis-Shevky tube add

2 5 cc of Tsuchiya reagent Mix the fluids by inversion, let stand 10 min and then centrifuge for 10 min at 1 600 r p m

Tsuchiya reagent is made by dissolving 15 Gm of phosphotungstic acid in about 500 cc of 95% ethyl alcohol Add 50 cc of concentrated hydrochloric acid and make up to 1 L with alcohol

The column of protein precipitate is measured along the narrow stem of the tube, if it is more than 0 4 cc, the urine should be diluted and the determination repeated The height of the column × 7 2 × the urine dilution equals the protein content in Gm /L. Protein in Gm /24 hr is found as

$$\text{Gm/L} \times \frac{\text{urine volume}}{1\,000} \times \frac{24}{\text{hours of collection}}$$

5 The specific gravity as measured and corrected for temperature is then corrected for protein content by subtracting 0 003 for each Gm /100 cc (10 Gm /L) The value found is maximal non protein urinary specific gravity

Sediment count—The count is done by enumeration of the formed elements of the sediment in a hemocytometer chamber Acidification and concentration of urine incident to the measurement of concentrating power tend to preserve the sediment (hyaline casts dissolve in alkaline and red cells in hypotonic urine) If for any reason only the count is desired it may be done from a fresh specimen collected over any desired (3 6 12 hr) period In such a case it is best to rinse out the collection bottle with formalin* before the test

Place 10 cc of urine in an Addis sediment tube Centrifuge together with the Addis Shevky tube used in protein estimation If there is a heavy precipitate of salts, pour off the supernatant resuspend the sediment in 0 9% saline and centrifuge again for 10 min at 1 600 r p m

After centrifuging estimate from the volume of the sediment the volume of supernatant in which it is to be suspended before counting (e g 0 1 0 2 0 4 even 1 0 or more cc) The suspension

is carefully made with an applicator stick. Each chamber of a standard hemocytometer is then filled with suspension

CAST COUNT Under low power with the light well cut down all the large fully enclosed ruled squares (the area used in white blood cell counts) are searched for casts. The area searched is 18 sq mm (9 sq mm. on each side of the hemocytometer) The number of casts counted is then divided by 18 to indicate the cast count/sq mm. Casts are noted as hyaline finely granular (this difference is more a matter of concentration and acidity of urine than of clinical interest) coarsely granular cellular (red white epithelial) pigment and renal failure casts. If no casts are found in the two sides the hemocytometer is freshly charged and the search repeated. With the sediment diluted in 0.2 cc. and urine volume of 500 cc in 12 hr absence of casts in 36 sq mm. of counting chamber surface indicates less than 2 700 casts/12 hr i e., less than are usually significant.

CELL COUNT The cells counted are red blood cells and then white plus epithelial cells squamous epithelium is not counted. The count is done under the high dry power with increased illumination It is necessary to focus up and down by means of the microscope s fine adjustment during the count because the cells do not settle out on the floor of the chamber as they do in blood counts

The cells are counted in the central ruled squares on each side of the hemocytometer (the areas used in red cell counts) The area counted is 2 sq mm Depending on urine volume it may be desirable to clean and recharge the chambers with suspension so that the area counted is increased until pathologic levels of red or white cell excretion are clearly absent. The cell count in each series divided by the area surveyed indicates the red and white plus epithelial cell count/sq mm

CALCULATION The sediment excretion is most easily calculated by reference to Hines s nomograph (Fig 17) The data necessary are volume of urine, hours of collection, volume in which

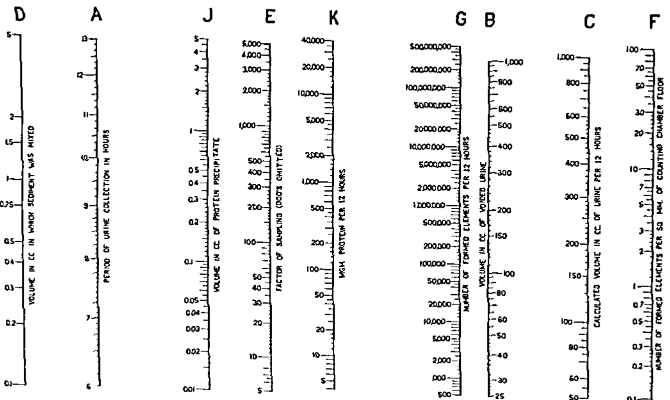


FIG 17 —Nomograph for the count of urine sediment (Addis) Description on page 371 (Courtesy of D C Hines Am J M Sc 187 841 1934)

sediment was suspended and number of elements/sq mm. of counting chamber floor Alternatively the following formula may be used

$$\frac{\text{urine vol in cc.} \times 12}{\text{hours of collection}} \times \frac{\text{vol. of suspension}}{10} \times \text{elements/sq mm.}$$

Results are expressed in units (casts red white plus epithelial) per 12 hr

Interpretation—The interpretation of the concentration test is considered on pages 271 ff It is important to make sure that the patient has understood and complied with the instructions and that there is neither receding edema (measurable by weighing before and after fluid restriction) nor prolonged protein and salt undernutrition (such as occurs during the rice diet) Although the pitressin* tests are not as critical in differentiating early failure of concentrating power such tests may be desirable in conditions which invalidate or contraindicate the concentration test. In patients with coronary artery disease use of pituitary extract may be dangerous

The upper limit of normal proteinuria is taken as 0 2 Gm./24 hr Normal values in the sediment counts are listed on page 268

FIG 1 —To use the nomograph place a straightedge across two designated scales intersecting them at given values, and read at the intersection with a third scale a derived value The scales *A* *B* *D* *F* and *J* include the original data obtained in the study of the urine The scales *C* *E* *G* and *K* give derived data To calculate the count of the urine sediment

1 Using scales *A* and *B* obtain a value on scale *C*

2 Using the newly found point on scale *C* in connection with scale *J* read from scale *K* (Scale *K* applies to Dr Addis modified technic for protein, using a 6 5 ml graduated centrifuge tube For the original technic using a 13 ml. tube divide the obtained value by 2)

3 Using scales *C* and *D* read from scale *E*

4 Connecting the obtained point on scale *E* with successive points on scale *F* read from scale *G* the values for the respective formed elements.

Formulas for checking $C = \frac{12B}{A}$ $G = 1\,000\ CDF$ $K = 7\,2\ CJ$

II UREA CLEARANCE

PRINCIPLE This test measures the volume of blood whose urea content is equivalent to that excreted in urine in 1 min Urea is excreted by glomerular filtration and partial tubular reabsorption Under suitable conditions the factor of reabsorption becomes relatively constant, so that the significant variable measured by the urea clearance is the rate of glomerular filtration

COLLECTION OF URINE AND BLOOD

The patient is told to take 2 glasses of water on retiring the night before the test and 2 more glasses at 7 and again at 8 o clock the morning of the test He need not fast The test period begins at 9 A M when the patient is given another glass of water and voids, emptying the bladder completely This specimen is discarded and the time noted to the nearest minute The patient then lies down or rests quietly in a comfortable chair He voids again about 10 A M The time is noted to the nearest minute and the specimen is saved and marked U_1 with the time of voiding Blood is taken from a vein (5 cc in oxalated or heparinized tube avoid ammonium oxalate) or as is sometimes necessary in children 0 2 cc from finger foot or ear lobe (micro method) The patient is given another glass of water again lies or rests quietly for an hour The time of the last voiding at about 11 A M is noted to the nearest minute and the specimen labeled U

It should be obvious that the hours given are suggestions only and can be varied to suit the convenience of the patient and laboratory The purpose is to secure adequate hydration before the test so that the test is done under conditions of rapid steady rate of urine flow For best results each specimen should have a volume of 2 oz or more and the volume of the first should be equal to or greater than that of the second If the volume of the first is considerably less than that of the second indicating a rapidly rising rate of urine

flow urine collection should be carried on for a third hour The original first specimen can then be discarded and the second and third sent for analysis In some conditions it is impracticable to establish *satisfactory water diuresis* (congestive heart failure hepatic cirrhosis acute glomerulonephritis) then the test must be done on *small volumes* of urine The disadvantages of this are (1) the fraction of urea reabsorbed in the tubules is increased and (2) errors due to incomplete bladder emptying are exaggerated. When such conditions exist and when there is known to be residual urine a single specimen should be collected by catheterization for 60–90 min

Measurement of urea clearance in night urine has been advocated by Landis The specimen is collected between the last voiding before going to bed and the time the patient comes to the laboratory for blood sampling in the morning Advantages of the method are (1) the patient does not have to be at the hospital clinic or laboratory during the urine collection (2) no special hydration is necessary and (3) errors due to residual urine are minimized by the relatively large volume of urine Disadvantages are (1) the test is done under conditions which usually establish a slow rate of urine flow (less than 1 *cc/min*) *so that the results are* somewhat lower than those obtained by the customary method (2) the time of urine collection is dependent on the patient's recollection (3) the blood urea concentration assumed to be constant during the time of collection may in fact vary appreciably in patients with renal disease (4) although the laboratory may rejoice in the reduction of the number of urine urea analyses by 1 the possibility of undetected error is automatically increased

PROCEDURE

The urine volume is measured and the volume of flow (cc/min) calculated for each specimen The urine is then *appropriately* diluted for analysis

URINE FLOW AND URINE DILUTION

URINE FLOW CC /MIN	DILUTION	DILUTION AFTER PROTEIN PRECIPITATION
<0 2	1 1 000	1 50
0 2–0 5	1 750	1 35
0 5–1 0	1 500	1 25
1 0–2 0	1 250	1 15
2 0–4 0	1 200	1 10
4 0–9 0	1 100	1 5

Principle The method suggested is a modification in particulars of the method of Archibald Urea condenses with α isonitroso propiophenone to yield a red color Under suitable conditions the color yield is proportional to urea content, while the interfering substances in blood and urine do not contribute to a sensible error The color is unstable to light Consequently in our modification it is developed in Corning Low Actinic test tubes, in which it is stable for long periods

a) *Protein precipitation* (Somogyi)

REAGENTS (1) 0 3N Ba(OH) (2) 5% $ZnSO_4 7H_2O$ The solutions are adjusted so that 10 cc of the $Ba(OH)_2$ neutralizes 10 cc of the $ZnSO_4$ solution Titration is done dropwise with phenolphthalein as indicator The end point is a pink color which persists for 1 min

PROCEDURES 1 Blood (macro 1/20 dilution) To 15 cc of water add 1 cc whole blood Mix and let stand until hemolyzed Add 2 cc of 0 3N Ba(OH) followed by 2 cc of $ZnSO_4$ solution Stopper Mix by shaking Let stand for 10 min Filter or centrifuge

2 Blood (micro 1/50 dilution) To 9 cc of water in a centrifuge tube add 0 2 cc blood Mix and hemolyze Add 0 4 cc of Ba(OH) solution and then 0 4 cc of $ZnSO_4$ solution Stopper Mix Let stand 10 min and centrifuge

3 Urine For protein rich urine add 1 cc of urine to 18 cc of water and in succession 0 5 cc each of barium and zinc solutions Mix and centrifuge The de proteinized supernatant is then diluted appropriately (Table)

b) Color development

REAGENTS. (1) Sulfuric phosphoric acid mixture concentrated sulfuric acid 1 volume syrupy (85%) phosphoric acid 3 volumes, water 1 volume (2) α isonitrosopropiophenone 4 Gm reagent in 100 cc. of 95% alcohol

PROCEDURE. Pipet a volume of filtrate or urine dilution which contains about 0 02 mg urea N into a Corning Low Actinic glass test tube (18 × 150 mm) This volume is about 3 cc. of 1 20 filtrate in normal bloods and correspondingly less in azotemic blood. In micro filtrates 5 cc is used of the urine dilutions indicated in the table 5 cc. is used. If less than 5 cc is added the volume is made up by addition of water

Next, add 4 cc of sulfuric phosphoric acid mixture and mix by tapping the tube on the palm of the hand Then add 0 3 cc. of the solution of α isonitrosopropiophenone Mix

Stopper the tube firmly with a rubber stopper which has been pierced with thick walled capillary tubing

Place the tube in a boiling constant level water bath for 90 min

Cool in water at 25 C for at least 15 min

Read color density in an appropriate spectrophotometer The apparatus we use is a Coleman Junior Spectrophotometer Model 6A cuvette 6-302 wavelength setting 540

UREA STANDARDS. These may be prepared from solutions containing 0 2 0 4 and 0 6 mg urea N per 100 cc and run simultaneously with the unknowns Or values may be read from a calibration curve When standard solutions are used, the concentration of urea N in the unknown may be calculated by referring to the standard solution nearest in color density thus where D = color density

$$\frac{\text{conc. of unknown in urea N}}{\text{conc of standard}} = \frac{D\ \text{unknown}}{D\ \text{standard}}$$

$$\frac{\text{conc. of unknown} \times \text{dilution} \times 5}{\text{vol of unknown added in cc.}} = \text{mg. urea N/100 cc.}$$

CALCULATION The basic formula for clearance calculation is $UV/B = C$, where U is urinary concentration in mg/cc, V, urine volume (cc/min) and B, blood concentration in mg/cc The product UV indicates urinary excretion in mg/min and the ratio UV/B indicates the volume of blood equivalent to this excretion, i e, the volume of blood cleared of the substance in question This formula applies to urea clearances when V is over the aug mentation limitation, 2 cc./min (maximal clearance or C_m) When V is less than 2 cc/min urea clearance falls because of increased urea reabsorption In this circumstance the clearance is calculated as $U\sqrt{V}/B$ and the datum is indicated as C_s (standard clearance) The correction obtained by using $\sqrt{V}$ is arbitrary and does not apply with precision in many conditions The setting of the aug mentation limit at 2 cc/min is also empiric However these formu lations suffice for clinical purposes when results are expressed in terms of per cent normal Normal maximal clearance is 75 cc/min Consequently, measured maximal clearance is reported as $C_m \times \frac{100}{75} = C_n \times 1\,33$ per cent of normal Normal standard clearance is taken as 55 cc/min so that the result of such a test is reported as $C_s \times 1\,84 =$ per cent normal Advantages of measurement of maximal rather than standard clearances are con sidered in the text (p 277) When the patient s body size differs significantly from the normal a correction should be made by multiplying the result of the test by 1 73 and dividing by the patient s surface area calculated from height and weight

III MEASUREMENT OF MANNITOL AND P AMINOHIPPURATE PLASMA CLEARANCES AND TMPAH

COLLECTION OF URINE AND BLOOD

Patients are freely hydrated and if apprehensive are given 0 3 Gm (1½ gr) of seconal sodium* 1 hr before the test is begun

APPARATUS.

Catheter tray with plain rubber catheters and with 1 each 12 and 14 F silk catheters with Coude tip
Bowl and sterile saline 1% for bladder washing
Intravenous set 250 cc. salvarsan flask with tubing, glass needle adaptor and Murphy drip
Sterile pyrogen free saline or water 500 cc.
Tunnel clamp for controlling rate of flow
20 gage needle for intravenous drip
22 gage needles for blood sampling
Heparinized flasks for blood samples (each contains about 22 units of heparin, i.e 0 2 cc of a water solution of heparin containing 110 units/cc. dried in the flask)
10 cc. syringes

PROCEDURE 1 Blood blank (B_0) Collect 10 cc of blood in a syringe through a 20 gage needle (for hematocrit, mannitol and PAH plasma blanks)

2 Priming infusion is started through the same needle This solution is intended to raise the plasma concentrations of PAH and mannitol rapidly to the desired levels It is made up in the flask by mixing 50 cc of 25% mannitol 4 cc of 20% PAH Na (sodium p-aminohippurate) and making up to 100 cc with saline or water It is run in at a rate of about 10 cc/min. During this time the catheter is placed and anchored with adhesive

3 Sustaining infusion As the priming infusion approaches the end of the flask the rate of flow is slowed to about 4 cc/min The sustaining infusion is mixed in the flask as the priming flows out. It contains 85 cc of mannitol solution 10 cc of PAH Na and is made up to 200 cc with saline or water It is infused at a rate of 4 cc/min

4 At the end of 5 min of sustaining infusion the urine is withdrawn from the bladder with a 50 cc syringe The bladder is rinsed with 3 successive 50 cc portions of saline The last rinse is expelled by injecting air and withdrawing it by suprapubic pressure This urine and the washings are discarded

5 The first blood sample (10 cc) is withdrawn about 4 min after the start of the urine collection

6 The bladder is emptied at about 10 min The time of the last rinse is noted to the nearest quarter minute The specimen is labeled U_1

7 The second specimen of urine is collected as was the first about 10 min later Time is noted and the specimen labeled U

8 At about 4 min in the third period the second blood is collected

9 The third urine is collected at about 10 min in the third period

10 The tubing is clamped tightly just below the Murphy drip A place near the needle adaptor is cleansed with alcohol and 50 cc of 20% solution of PAH Na is injected into the tubing in about 5–7 min The patient should be warned that he will feel a sensation of heat or a desire to expel flatus but that nothing more untoward will occur

11 To the infusion fluid remaining in the flask is added 36 cc of 20% solution of PAH Na the clamp is released and the flow rate readjusted to about 4 cc/min Infusion is continued for 5 min more

12 The bladder is again washed out and urine plus washings discarded

13 The third blood is collected at about 4 min

14 The fourth urine specimen is collected at about 10 min

15 The fifth urine is collected at about 10 min

16 The fourth blood is collected at about 4 min in the sixth urine period

17 The sixth urine is collected at about 10 min This collection ends the test The infusion is discontinued and the catheter withdrawn

On the record sheet which notes times of urine and blood collections and the course of the test (pain difficulty in collecting

urine, etc) should also be noted the patient s blood pressure before and twice during the procedure Height, weight blood urea and plasma total protein content should be recorded on the same sheet Doses of mannitol and PAH are suitably adjusted for major abnormalities of renal function or of body size

ANALYTIC PROCEDURES

1 *Preparation of plasma filtrations*

a) Cadmium filtrate (Fujita and Iwatake)

REAGENTS. (1) $CdSO_4$ solution 34 67 Gm $3\,CdSO_4\,8\,H_2O$ 169 3 cc 1N H_2SO_4 and water to 1 L. (2) 1 1N NaOH

METHOD To 15 cc of water add 1 cc of plasma and 3 cc. of $CdSO_4$ solution and mix Add 1 cc of 1 1N NaOH Stopper Shake filter or centrifuge

b) Somogyi Ba Zn filtrate 1/20 as described under urea method applies equally well

2 *Determination of mannitol* (Corcoran and Page)

Principle Mannitol is oxidized by periodic acid to yield formic acid and formaldehyde Glucose although attacked, yields little formaldehyde The excess periodic acid is reduced by addition of stannous chloride The formaldehyde yield is determined colorimetrically by an adaptation of the method of MacFadyen

REAGENTS (1) Periodic acid reagent (0 03M in 0 25M H_2SO_4)

(2) Stannous chloride (prepared daily) Approximately 2 85 Gm reagent grade $SnCl_2$ is dissolved in 100 cc. 2 5N HCl This solution is titrated against the KIO_4 and adjusted so that 10 cc of the stannous chloride reagent is equivalent to 10 2 cc of periodic acid reagent (starch iodine indicator)

(3) Chromotropic acid reagent (prepared daily) To 0 2 Gm chromotropic acid (1 8 dihydroxynaphthalene 3 6-disulfonic acid) placed in a 100 cc volumetric flask is added 4 0 cc water to dissolve it The reagent is made up to 100 cc by adding 15M H_2SO_4

PROCEDURE Place 2 0 cc of sample (filtrate or urine dilution the latter usually 1/100 in water or 1/50 if excretion is depressed) in a tall test tube calibrated at 25 cc (e g Lewis and Benedict blood sugar tubes) The sample should contain 0 5–3 0 mg mannitol/100 cc To this add 0 5 cc of the KIO_4 reagent. Mix and allow to stand for 8–10 min Add 0 5 cc of the stannous chloride reagent Mix Add 5 cc of the chromotropic acid from a free delivery refill burret or pipet Mix the contents by tapping them against the palm of the hand Place in a boiling water bath for 30 min

A reagent blank is set up containing 2 cc of water plus reagents

A plasma blank (oxidized) is set up in the foregoing manner from B_0

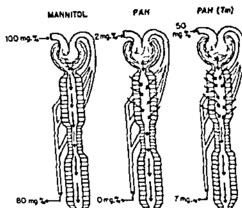
A plasma blank (unoxidized) is set up from B_0 In this case the stannous chloride is added first and the periodic acid reagent second

After the tubes have been heated they are cooled in running water placed in a water bath at about 25 C and diluted to 25 cc with water The temperature is allowed to equilibrate at 25 C for another 30 min

The color densities are then determined in the Coleman Junior Spectrophotometer (6 300 or 6 302 cuvette wavelength 570) Water standards may be run simultaneously with the unknowns (0 5 1 2 4 mg mannitol/100 cc) or the concentration may be found by reference to a calibration curve

CALCULATION Concentrations in urine are found directly by reference to water standards or calibration curve Plasma levels are found by subtracting from the densities of the sample the color density of the unoxidized plasma blank The difference between oxidized and unoxidized plasma blanks is taken as plasma mannitol blank and this value is expressed as mannitol as is also the apparent mannitol content of the unknowns The plasma mannitol blank is then subtracted from the unknowns and the unknowns multiplied by the dilution factor (usually 1/20) Thus if the density

difference between oxidized and unoxidized plasma blanks equals 0.2 mg mannitol/100 cc. and the apparent concentration in the 1/20 filtrate of B_1 is 2.3 mg/100 the true mannitol content of the filtrate is 2.1 mg/100 cc. and the mannitol content of the plasma 42 mg/100 cc.



FILTERED	120 mg/min.	0.42 mg/min	10 mg/min
SECRETED	0 mg/min.	13.6 mg/min	80 mg/min.
REABSORBED	0 mg/min.	0 mg/min	0 mg/min
EXCRETED	120 mg/m	14 mg/min	90 mg/min
PLASMA CLEARANCE	20 cc./min	700 cc/min.	180 cc./min.

FIG. 18.—*Diagrams to show principles of mannitol and PAH clearance and of Tm measurement* The conventions used are similar to those for inulin and diodrast[a] (p. 81) (Modified from "Sharp and Dohme Seminar," vol. 9, 1947.)

Plasma mannitol clearance is found as UV/B where U is urinary mannitol (mg/cc.) V volume of urine plus washings in cc/min and B the plasma mannitol concentration in mg/cc. Since at usual rates of urine flow about 10% of filtrable mannitol is reabsorbed in the tubules glomerular filtration rate (GFR) is estimated as the mannitol clearance × 1.1 This value is corrected

for surface area by multiplying it by 1 73 divided by the body surface in sq m

3 *Determination of p aminohippuric acid (PAH) and Tm(PAH)*

Principle The p amino group is diazotized and coupled with the chromophore (1 naphthyl ethylenediamine) in the presence of ammonium sulfamate The method is an adaptation of that used in measuring sulfonamide drugs PAH clearance is therefore somewhat inaccurate in patients receiving such medication In these cases, diodrast® can be advantageously substituted for PAH Diodrast® iodine is measured by the method of Corcoran and Page

REAGENTS (1) Sodium nitrite, 100 mg/100 cc Prepared every 3 days (2) Ammonium sulfamate, 500 mg/100 cc Prepared every 2 weeks (3) 1 2N hydrochloric acid (4) N(1 naphthyl) ethylenediamine dihydrochloride 100 mg/100 cc This solution is stored in the refrigerator in a brown bottle

PROCEDURE To 10 cc of plasma filtrate or a dilution thereof, or of diluted urine containing about 0 15 mg PAH/100 cc add 2 cc of 1 2N HCl mix and add 1 cc of $NaNO_2$ reagent Mix Let stand for 3–5 min Add 1 cc of ammonium sulfamate Mix Let stand 3–5 min Add 1 cc of N(1 naphthyl) ethylenediamine dihydrochloride Mix and let stand 30 min

The color densities are then read at 540 wavelength in a 6 302 cuvette A reagent blank is prepared from 10 cc of water plus the above reagents A plasma blank is also found for B_0 Calculation of concentration is made by reference to a curve prepared from a standard solution of PAH acid

For plasma concentrations of about 2 mg/100 cc 10 cc of 1/20 filtrate is used for concentrations of about 4 mg/100 cc 5 cc and so on The Tm plasma concentrations of about 50 mg/100 cc are measured by using 10 cc of a 1/25 water dilution of the plasma filtration For urine samples 2 cc of 1/100 dilution of urine is made up to 10 cc for analysis In the Tm periods the 1 100 dilution is diluted 1/10 and 2 cc is used for analysis made

up to 10 cc in the test tube Dilutions are decreased in urine as renal function fails (estimated from blood urea N)

CALCULATION Plasma PAH clearance at low plasma concentration is calculated as UV/B and the result corrected to 1 73 sq m body surface Under most circumstances this value is equivalent to renal plasma flow Renal blood flow is calculated as plasma PAH clearance/1 — hematocrit.

At high concentrations the measurement desired is Tm_{PAH} In essence the calculation consists in subtracting from total minute urinary PAH the PAH contributed by filtration. Only about 83% of plasma PAH is filtrable The residual 17% is bound to protein Consequently filtered PAH is calculated as $0.83 \times P_{PAH} \times$ glomerular filtration rate Alternatively

$$Tm_{PAH} = C_{PAH} - (0\,83 \times GFR)\ P_{PAH}$$

where C_{PAH} is PAH plasma clearance at high concentrations. This value is then corrected for surface area

In summary direct observations made by these methods are

1 Renal blood flow (RBF) = $C_{PAH}/1$ — hematocrit
2 Renal plasma flow (RPF) = C_{PAH} at low concentrations
3 Glomerular filtration rate (GFR) = C_{in} C_{thios} i e $C_{mannitol} \times 1\,1$
4. $Tm_{PAH} = UV_{PAH} - 0\,83\ P_{PAH}\ GFR$

Derived values are

5 Filtration fraction = GFR/RPF
6 RBF/Tm_{PAH} RPF/Tm_{PAH}
7 GFR/Tm_{PAH}
8 Renal resistances

a) Over all Pm/RBF or (Pm — 10)/RBF Pm is *the mean* of the systolic and diastolic arterial pressures Pm — 10 is sometimes preferred as a closer approximation to mean arterial pressure

b) Resistance per unit Tm e g., Pm/RBF/Tm_{PAH} or (Pm—10)/RBF/Tm_{PAH}

for surface area by multiplying it by 1 73 divided by the body surface in sq m

3 *Determination of p aminohippuric acid (PAH) and Tm(PAH)*

Principle The p amino group is diazotized and coupled with the chromophore (1 naphthyl ethylenediamine) in the presence of ammonium sulfamate The method is an adaptation of that used in measuring sulfonamide drugs PAH clearance is therefore somewhat inaccurate in patients receiving such medication In these cases, diodrast® can be advantageously substituted for PAH Diodrast® iodine is measured by the method of Corcoran and Page

REAGENTS (1) Sodium nitrite 100 mg/100 cc Prepared every 3 days (2) Ammonium sulfamate, 500 mg/100 cc Prepared every 2 weeks (3) 1 2N hydrochloric acid (4) N(1 naphthyl) ethylenediamine dihydrochloride 100 mg/100 cc This solution is stored in the refrigerator in a brown bottle

PROCEDURE To 10 cc of plasma filtrate or a dilution thereof or of diluted urine containing about 0 15 mg PAH/100 cc add 2 cc of 1 2N HCl, mix and add 1 cc of $NaNO_2$ reagent Mix Let stand for 3–5 min Add 1 cc of ammonium sulfamate Mix Let stand 3–5 min Add 1 cc of N(1 naphthyl) ethylenediamine dihydrochloride Mix and let stand 30 min

The color densities are then read at 540 wavelength in a 6 302 cuvette A reagent blank is prepared from 10 cc of water plus the above reagents A plasma blank is also found for B_0 Calculation of concentration is made by reference to a curve prepared from a standard solution of PAH acid

For plasma concentrations of about 2 mg/100 cc 10 cc of 1/20 filtrate is used for concentrations of about 4 mg/100 cc 5 cc and so on The Tm plasma concentrations of about 50 mg/100 cc are measured by using 10 cc of a 1/25 water dilution of the plasma filtration For urine samples 2 cc of 1/100 dilution of urine is made up to 10 cc for analysis In the Tm periods the 1 100 dilution is diluted 1/10 and 2 cc is used for analysis made

up to 10 cc. in the test tube Dilutions are decreased in urine as renal function fails (estimated from blood urea N)

CALCULATION Plasma PAH clearance at low plasma concentration is calculated as UV/B and the result corrected to 1 73 sq m. body surface. Under most circumstances this value is equivalent to renal plasma flow Renal blood flow is calculated as plasma PAH clearance/1 — hematocrit.

At high concentrations the measurement desired is Tm_{PAH} In essence the calculation consists in subtracting from total minute urinary PAH the PAH contributed by filtration. Only about 83% of plasma PAH is filtrable The residual 17% is bound to protein Consequently filtered PAH is calculated as 0.83 × P_{PAH} × glomerular filtration rate Alternatively

$$Tm_{PAH} = C_{PAH} - (0\ 83 \times GFR)\ P_{PAH}$$

where C_{PAH} is PAH plasma clearance at high concentrations This value is then corrected for surface area.

In summary direct observations made by these methods are

1 Renal blood flow (RBF) = C_{PAH}/1 — hematocrit
2 Renal plasma flow (RPF) = C_{PAH} at low concentrations
3 Glomerular filtration rate (GFR) = $C_{\text{in ul}}$ $C_{\text{thios lf e}}$ $C_{\text{mann tol}}$ × 1 1
4 $Tm_{PAH} = UV_{PAH} - 0\ 83\ P_{PAH}$ GFR

Derived values are

5 Filtration fraction = GFR/RPF
6 RBF/Tm_{PAH} RPF/Tm_{PAH}
7 GFR/Tm_{PAH}
8 Renal resistances

a) Over all Pm/RBF or (Pm — 10)/RBF Pm is the mean of the systolic and diastolic arterial pressures Pm — 10 is sometimes preferred as a closer approximation to mean arterial pressure

b) Resistance per unit Tm e g Pm/RBF/Tm_{PAH} or (Pm—10)/RBF/Tm_{PAH}

c) Localization of resistance (Lamport), i e, R_A (afferent tract resistance or resistance from aorta to the end of the glomerular capillaries) and R_L (resistance in efferent tract) These resistances may be calculated either from the observed RBI or from RBF/Tm_{PAH}

Strict interpretation of the resistance formulas is probably futile However, they serve a purpose in that they integrate into the estimate of renal function the level of arterial pressure

BIBLIOGRAPHY

ARCHIBALD R. Colorimetric determination of urea J Biol Chem 157 507 1945

CORCORAN A C AND PAGE I H A method for the determination of mannitol in plasma and urine J Biol Chem 170 165 1947

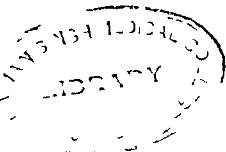
——— Determination of the diodrast® iodine in urine and in filtrates of plasma, J Lab & Clin Med 28 1514 1943

HINES D C. A nomograph for simplifying computation of the urine sediment count (Addis) Am J M Sc 187 841 1934

LAMPORT H Improvements in calculation of renal resistance to blood flow J Clin Investigation 22 461 1943

SMITH H W FINKELSTEIN N ALIMINORA L CRAWFORD B AND GRABER M. The renal clearances of substituted hippuric acid derivative and other aromatic acids in dog and man J Clin Investigation 24 388 1945

SOMOGYI M Determination of blood sugar J Biol Chem 160 69 1945



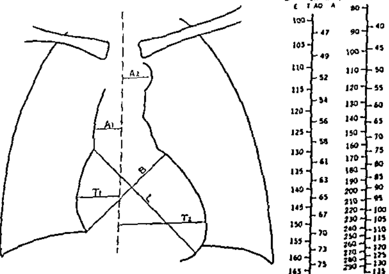


Fig 19 (*left*) —Diameters for measuring size of the heart A_1 plus A_2 transverse diameter of aortic arch T_1 plus T_2 transverse diameter of heart *L*, long diameter *B* broad diameter (*Courtesy of H E. Ungerleider and R. Gubner Am Heart J 24 494 October 1942*)

Fig 20 (*right*) —Predicted transverse diameter of the heart (left side of scale) or aortic arch (right side of scale) from weight and height As indicated a correction for age is necessary for the aortic diameter Values exceeding 10 per cent of those predicted for any of these measurements are abnormal (Courtesy of H E. Ungerleider and R. Gubner Am. Heart J 24 494 October 1942)

Appendix 3 LOW SODIUM DIET

TOTAL DAILY FOOD ALLOWANCE

2 servings fruit (from list)
1 serving cereal (from list)
5 slices bread (unsalted)
6 squares butter (unsalted)
1 qt salt free milk
1 egg

3 oz meat (from list)
½ cup potato or rice
2 servings vegetable (from list)
2 servings dessert (from list)
3 tablespoons white sugar

To this may be added
1 slice bread or
2 servings fresh fruit or
2 servings beverage or
2 servings sweets (from list)

SAMPLE MENU

Breakfast
½ cup orange juice
1 cup cooked oatmeal
2 slices salt free bread
2 squares salt free butter
½ cup liquid salt free milk
Black coffee

Luncheon
1 poached egg
½ cup steamed rice
1½ slices salt free bread
2 squares salt free butter
1 small baked apple
1 cup liquid salt free milk
1 serving dessert (from list)

Dinner
3 oz broiled fresh fish
½ cup frozen asparagus
1 cup sliced tomatoes
1½ slices salt free bread
1 serving dessert (from list)
2 squares salt free butter
½ cup liquid salt free milk

Between meals Allowable additions (½ cup is average serving)
All fresh fruits (raw and cooked) and fruit juices
Canned dried or frozen fruits and juices (unless label states that salt or sodium benzoate has been added)

VEGETABLES
1 serving ½ cup

All vegetables in the following list may be used with vinegar lemon juice salad oils or any of the permissible seasonings in list of condiments

Fresh

Asparagus	Beans green	Beans lima	Broccoli
Brussels sprouts	Cabbage	Carrots	Cauliflower
Corn	Cowpeas	Cucumber	Eggplant
Endive	Lettuce	Macaroni	Mushrooms
Okra	Onions	Parsley	Parsnips
Peas	Potato	Pumpkin	Radishes
Rice	Soybeans	Spaghetti	Squash (all kinds)
Tomatoes	Turnips (white yellow)	Turnip leaves	

Fro en
Asparagus Beans, green Brussels sprouts Cauliflower
Corn
D ied
Beans, navy Soybeans

Meats

1 serving is 3 oz. t measures 6 X 3 4 X 4 n.

Meat may be fried in lard or unsalted vegetable fats or oils.

Beef (fresh or frozen)	Oysters (fresh)
Lamb (fresh or frozen)	Chicken (fresh)
Pork (fresh or frozen)	Duck
Rabbit (fresh or frozen)	Turkey
Veal (fresh or frozen)	Quail
Fish (fresh)	

Cereals

1 serv ng is 1 cup ooked or 2 cups prepared

Barley pearled	Corn meal	Cracked wheat	Farina plain
Instant Ralston	Maltex	Oatmeal (rolled oats)	Pettijohn s
Puffed rice	Puffed wheat	Rice	Shredded wheat
Wheat germ	Wheatena		

Beverages

1 glass is 8 oz.

Apple juice	Coffee	G nger ale	Grape juice
Grapefruit juice	Lemonade	Orange juice	Orange crush
Pineapple juice	Postum	Prune juice	Tangerine juice
Tea			

Reconstituted salt free m lk, plain or flavored with unsweetened chocolate vanilla, caramel fresh pineapple strawberry or banana.

Desserts

1 serv ng is ½ cup

Cornstarch puddings
Gelatin desserts made w th plain gelatin, fruits and juices
Fruit tapioca puddings
Rice with fruit and sugar

Sweets

Cand es should be made with white sugar and salt free milk.

Honey
Homemade candies
Home canned jams jell es marmalades
Popcorn with syrup
Hershey s chocolate syrup

Condiments and Flavoring

Allspice	Caraway	Cinnamon	Curry powder
Garl c	Ginger	Lemon extract	Lemon juice
Mace	Mustard powder	Nutmeg	Paprika
Pepper black	Pepper red	Pepper white	Peppermint extract
Sage	Sugar white	Thyme	Tumeric
Van lla extract	V negar	Walnut extract	Sod um free salt substitutes"

Fats

Crisco	Spry
Lard	Any unsalted pure food oil

Miscellaneous Foods

Unsalted nuts	Unsalted popcorn

Bread Substitutes

Low sodium caraway seed bread	Low sodium cinnamon roll
Special Passover or thin tea matzoth	

Recipe for salt free bread

1¾ lb flour	2 oz unsalted shortening
2½ oz sugar	1 pt water
1 oz yeast	

Follow the method for ordinary bread Bake in 400 F oven for 40 min Yield is 2 loaves

Sources of sodium to be avoided

1 Salt both at the table and in cooking and preparing food
2 Commercially processed foods in which salt has been added
   a) Smoked salt cured and other processed meats such as ham bacon salt pork sausages corned beef salt fish canned meats and fish bouillon cubes and meat extracts
   b) Cheese
   c) Pickled and spiced products such as olives pickles catsup sauces, sauerkraut salad dressings and prepared mustard
   d) Canned vegetables and soups
   e) Salted butter margarine peanut butter and cheese spreads
   f) Celery beets beet greens kale dandelion mustard greens spinach
   g) Celery salt onion salt garlic salt meat flavoring prepared horseradish Worcestershire sauce
   h) Ordinary bakery goods and crackers
   i) Prepared cereals other than those on cereal list
   j) All other salted foods such as pretzels potato chips popcorn salted nuts most candies and candy bars commercial jellies and jams
3 Soda products such as baking soda baking powder self rising flours, including pancake biscuit muffin and cake mixes also various laxatives and other remedies containing salts (consult physician before taking any medication)
4 Beer and wines (consult physician before using any alcoholic beverage)
5 Foods labeled salt free or salt restricted unless checked with dietitian
6 Water which has been run through water softening equipment

Index